| | | |
|---|---|---|
| PI: **Monson, Brian Bruce** | Title: Auditory experience during the prenatal and perinatal period | |
| Received: 10/28/2019 | FOA: PAR18-487<br>Clinical Trial:Optional | Council: 05/2020 |
| Competition ID: FORMS-E-REVISED | FOA Title: NIDCD Early Career Research(ECR) Award (R21 - Clinical Trials Optional) | |
| **1 R21 DC017820-01A1** | Dual: | Accession Number: 4367950 |
| IPF: 577704 | Organization: UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN | |
| Former Number: | Department: Speech and Hearing Science | |
| IRG/SRG: CDRC | AIDS: N | Expedited: N |
| Subtotal Direct Costs<br>(excludes consortium F&A)<br>Year 1: [redacted]<br>Year 2: [redacted]<br>Year 3: [redacted] | Animals: N<br>Humans: Y<br>Clinical Trial: N<br>Current HS Code: 30<br>HESC: N<br>HFT: N | New Investigator:<br>Early Stage Investigator: |
| | | |
| *Senior/Key Personnel:* | *Organization:* | *Role Category:* |
| Brian Monson | UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN | PD/PI |
| Derrick Rollo | Carle Foundation Hospital | Co-Investigator |
| Carolyn Brown | University of Iowa | Consultant |
| Sophie Ambrose | Boys Town National Research Hospital | Consultant |
| Brittney Reidy | University of Illinois at Urbana-Champaign | Other (Specify)-Clinical Pediatric Audiologist |
| Sa Shen | University of Illinois at Urbana-Champaign | Other (Specify)-Biostatistician |

*Additions for Review*

| | |
|---|---|
| Accepted Publication | Articles accepted for publication since application submission |

APPLICATION FOR FEDERAL ASSISTANCE
**SF 424 (R&R)**

| **3. DATE RECEIVED BY STATE** | **State Application Identifier** |
|---|---|
| | |

**1. TYPE OF SUBMISSION***

❍ Pre-application ● Application ❍ Changed/Corrected Application

**4.a. Federal Identifier**
R21DC017820

**b. Agency Routing Number**

**2. DATE SUBMITTED** | **Application Identifier**

**c. Previous Grants.gov Tracking Number**

**5. APPLICANT INFORMATION** **Organizational DUNS*:** [redacted]

Legal Name*: UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN
Department:
Division:
Street1*: Sponsored Programs Administration
Street2: [redacted]
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]

Person to be contacted on matters involving this application
Prefix: First Name*: Robin Middle Name: Last Name*: Beach Suffix:
Position/Title:
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: Email: [redacted]

**6. EMPLOYER IDENTIFICATION NUMBER** *(EIN) or (TIN)** [redacted]

**7. TYPE OF APPLICANT*** H: Public/State Controlled Institution of Higher Education

Other (Specify):
**Small Business Organization Type** ❍ Women Owned ❍ Socially and Economically Disadvantaged

**8. TYPE OF APPLICATION***

❍ New ● Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

**Is this application being submitted to other agencies?*** ❍Yes ●No What other Agencies?

**9. NAME OF FEDERAL AGENCY***
National Institutes of Health

**10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER**
TITLE:

**11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT***
Auditory experience during the prenatal and perinatal period

**12. PROPOSED PROJECT**
Start Date* Ending Date*
07/01/2020 06/30/2023

**13. CONGRESSIONAL DISTRICTS OF APPLICANT**
[redacted]

# SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE



**14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION**

Prefix: First Name*: Brian Middle Name: Bruce Last Name*: Monson Suffix:
Position/Title: Assistant Professor
Organization Name*: UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN
Department: Speech and Hearing Science
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: Email*: [redacted]

**15. ESTIMATED PROJECT FUNDING**

a. Total Federal Funds Requested* [redacted]
b. Total Non-Federal Funds* [redacted]
c. Total Federal & Non-Federal Funds* [redacted]
d. Estimated Program Income* [redacted]

**16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?***

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

**17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)**

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

**18. SFLLL or OTHER EXPLANATORY DOCUMENTATION** File Name:

**19. AUTHORIZED REPRESENTATIVE**

Prefix: First Name*: Avijit Middle Name: Last Name*: Ghosh Suffix:
Position/Title*: Comptroller
Organization Name*: University of Illinois at Urbana-Champaign
Department: Sponsored Programs
Division:
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: Email*: [redacted]

**Signature of Authorized Representative***
Brad Johnson

**Date Signed***
10/28/2019

**20. PRE-APPLICATION** File Name:

**21. COVER LETTER ATTACHMENT** File Name:CoverLetter.pdf

# 424 R&R and PHS-398 Specific
## Table Of Contents

OMB Number: 4040-0010
Expiration Date: 10/31/2019

# Project/Performance Site Location(s)

## Project/Performance Site Primary Location

○ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN
Duns Number: [redacted]
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]
Project/Performance Site Congressional District*: [redacted]

## Project/Performance Site Location 1

○ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Carle Foundation Hospital
DUNS Number:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]
Project/Performance Site Congressional District*: [redacted]

**Additional Location(s)** File Name:





Funding Opportunity Number: PAR-18-487. Received Date: 2019-10-28T12:08:58.000-04:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

# RESEARCH & RELATED Other Project Information

**1. Are Human Subjects Involved?*** ● **Yes** ❍ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If NO, is the IRB review Pending? ❍ **Yes** ● **No**

IRB Approval Date: 11-14-2018

Human Subject Assurance Number 00008584

**2. Are Vertebrate Animals Used?*** ❍ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number

**3. Is proprietary/privileged information included in the application?*** ❍ **Yes** ● **No**

**4.a. Does this project have an actual or potential impact - positive or negative - on the environment?*** ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

**5. Is the research performance site designated, or eligible to be designated, as a historic place?*** ❍ **Yes** ● **No**

5.a. If yes, please explain:

**6. Does this project involve activities outside the United States or partnership with international collaborators?*** ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

| | Filename |
|---|---|
| **7. Project Summary/Abstract*** | Project_Summary.pdf |
| **8. Project Narrative*** | Project_Narrative.pdf |
| **9. Bibliography & References Cited** | Bibliography.pdf |
| **10.Facilities & Other Resources** | Facilities_and_Other_Resources.pdf |
| **11.Equipment** | Equipment.pdf |





Funding Opportunity Number: PAR-18-487. Received Date: 2019-10-28T12:08:58.000-04:00

Within the United States alone, over a half-million infants are born premature each year. While medical advances have dramatically improved survival rates, long-term morbidities related to auditory function are common. The preterm population suffers from a relatively high prevalence of sensorineural hearing loss, auditory neuropathy/dys-synchrony, and central auditory processing disorder. Even preterm infants in whom no specific auditory pathology has been diagnosed exhibit cognitive impairments related to auditory processing, including auditory attention deficits, language processing deficits, and other speech/language communication deficits. Despite these facts, a solid understanding of the impact of premature birth on auditory neurodevelopment is lacking. Possible effects of the acoustic environment are unknown. The long-term objective of this research is to characterize the effect of premature birth on auditory neurodevelopment and communication behavior to aid in improving best medical practices and therapeutic interventions for preterm infants. In this study, we propose to measure the effects of auditory input during the preterm period on neurodevelopmental outcomes. There are three specific aims. In Aim 1 we will recruit a cohort of preterm infants in the neonatal intensive care unit (NICU) to prospectively measure their auditory input during hospital stay. We will quantify detailed auditory experience in the NICU and determine how this differs from intrauterine auditory experience. In Aim 2 we will determine the effect of premature birth on auditory function at 3 months of age. In Aim 3 we will determine the relationship between our measured parameters of perinatal auditory experience and auditory function in infancy. The proposed study will lay the foundation for a longitudinal study aimed to determine the effect of auditory experience in the NICU on long-term auditory and language development. Valuable insight will be gained as to how premature birth and NICU environment might affect auditory neurodevelopment. Results of these studies will ultimately aid in identifying (1) effective interventions to optimize NICU auditory experience and (2) potential early-intervention therapies for NICU infants at greatest risk for auditory and language deficits later in childhood.

Within the United States alone, over 500,000 infants are born preterm each year, with survivors commonly suffering from cognitive disorders and auditory neurodevelopmental disorders. This research will provide valuable insight as to how premature birth, medical care, and sounds in the neonatal intensive care unit affect brain development in preterm infants.

## FACILITIES AND OTHER RESOURCES

### University of Illinois at Urbana-Champaign (UIUC)

The University of Illinois at Urbana-Champaign (UIUC), located in east central Illinois, is home to over 50,000 students and nearly 3,000 faculty members. UIUC holds the Carnegie classification of Highest Research Activity and in the 2020 U.S. News & World Report's America's Best Colleges was ranked as the number 14 public university.

As one of 15 colleges and instructional units housed at UIUC, the College of Applied Health Sciences has the mission to, “advance research, instruction and public engagement that promotes the development of healthy, livable communities, facilitates optimal living with disability and promotes health and wellness across the lifespan and throughout a diverse society.” Within the college, the Center on Health, Aging, and Disability (CHAD) works to further this mission by supporting faculty research on these topics in a variety of ways including technical support for qualitative and quantitative research, educational opportunities with regard to grantsmanship, and acting as a liaison to the local community, specifically through their continued support of the Age-Friendly Champaign-Urbana effort.

Situated in the heart of the midwest and its rich history in communication sciences, the UIUC Department of Speech and Hearing Science is accredited by the Council of Academic Accreditation of the American Speech-Language-Hearing Association and boasts a top-20 ranking for graduate schools in speech language pathology. The department is home to many NIH- and other externally-funded investigators directing research programs spanning the broad spectrum of communication sciences and disorders.

### Technological Infrastructure

Advanced digital services are provided by Technology Services. Network resources that support the proposed project include category six (6) wiring with 100MB or 1Gb connectivity provided to all desktop computers (PC or Apple) and Wi-Fi (802.11 a/b/g/n) in all campus buildings and meeting rooms to connect computers and mobile devices. The computer network backbone offers a strong 10Gb bandwidth. The campus participates in the Internet2, MREN, and ESnet networks.

The Office of Information, Security and Technology (OIST) from the College of Applied Health Sciences checks that all necessary software is installed on all computers and includes Microsoft Office, forefront virus protection, Adobe Acrobat Suite (including Pro and Reader) along with desktop security and anti-malware software. An extensive IT support staff maintains all the computers, the computer network, constantly investigates on technology trends and maintains college wide services such as survey platforms, statistical processing software and online collaboration tools. In addition to project desktop-computing systems, daily backed up virtual machines and storage spaces are available to the project along with Webservers with Web Services support and are provided by College IT staff.

In terms of security and ability to handle medical health information, OIST provides guidance and support to facilitate the installation, configuration, and operation of UIUC-Amazon HIPAA virtual machine and storage. In addition, among OIST’s functionality is adequate support and physical space for video production and editing. Online collaboration tools are part of the technology assets that OIST offers to the project, such as BlackBoard Collaborate and RedCap, which will be instrumental in enabling and supporting interaction and data sharing among members of the project.

Conference and meeting facilities for the proposed project are provided by CHAD and the College of Applied Health Sciences. They include two regular conference rooms with dedicated AV projector systems. One videoconference room with a Tandberg 6000MXP IP (H.323) videoconference system that includes high-end performance features, dual large flatscreen monitors, dual TANDBERG Precision HD Cameras and CD-quality, stereo audio. An additional workshop facility provide seating 35 and contains a dedicated computer, document camera, and projector system along with an advanced Media:Scape collaborator desk system providing dual screen HD videoconferencing collaboration across the table with connection to teams across the globe.

CHAD also provides an enhanced “high end” poster printer (HP Designjet Z6200) for use by all AHS faculty. The poster printer is located in the Center on Health, Aging and Disability Main Office.

**Biostatistical Services**
CHAD provides research biostatistical support to all Applied Health Sciences faculty. The Research Biostatistician position is a twelve-month full-time position. The Research Biostatistician consults with individual faculty and investigative research teams as to appropriate research design, power analyses, and statistical approaches for grant applications, ongoing research projects and preliminary studies. Research biostatistician is located in CHAD and reports to the Director of the Center. Infrastructure support includes MS Office, Adobe Pro and full licenses to SPSS, SAS, M Plus, S Plus, DBMS File Transfer (Oracle) and MATLAB.

**Laboratory**
The PI has an office and laboratory space on UIUC campus. The lab holds a large 8 ft $\times$ 16 ft double-walled sound-treated booth that can be used for audiological testing, and is currently equipped for speech perception testing and psychoacoustics experiments. The lab has four computer workstations with acoustical analysis software. There is a LENA dedicated computer to run the LENA software and classification algorithm. There is currently 10 TB of upgradable storage on an encrypted and password-protected server for the LENA data storage.

**Carle Foundation Hospital**
The Carle Foundation Hospital has been engaged in clinical research for over 20 years and has a strong clinical research program facilitated by the Stephens Family Clinical Research Institute (SFCRI). The SFCRI includes eight individual research centers that focus on many different aspects of health and clinical research. The SFCRI employs full-time research staff to assist in all stages of research, including development of the proposal, institiutional review board application development, recruitment of subjects, and execution of the data collection plan.

Carle Foundation Hospital has a 48-bed Level III neonatal intensive care unit (NICU) with a newly constructed separate small baby unit for infants born <28 weeks’ gestation. The NICU physician and nursing staff have collaborated on multiple past and current research projects with investigators at UIUC. Relevant for the present study, Carle hospital averages over 120 very preterm infant (*i.e.*, born < 32 weeks’ gestation) admissions per year. Families of very preterm infant patients will be recruited through the Carle NICU. The PI and Co-I have access to the expertise and insight of the clinicians and nurses who regularly provide health care to these patients.

The PI’s lab and the Carle Hospital are within 10 blocks of each other (less than 5 min drive).

**Audiology Clinic**
The Speech and Hearing Science Department is home to the Audiology Clinic where the pediatric audiological assessments in this proposal will be conducted. The clinic has two double-walled sound-treated booths and equipment for conducting all standard audiological assessments.

**Resources for Early Stage Investigators**
The University, College, and Department offer a substantial number of institutional resources for junior faculty. Examples at the university level include a grant writing seminar series with mentored feedback and mock review, and campus research grant opportunities. The UIUC Center for Innovation in Teaching and Learning offers regular seminars and workshops, as well as individual consultations, for improving classroom teaching. The college’s CHAD holds frequent seminars focused on the promotion and tenure process, provides travel awards, and offers research grants to support collection of pilot data. Departmental support includes 40% protected research time, resources for classes, and a formal mentoring program within the department.

**Intellectual Environment**
The Champaign-Urbana community provides a rich intellectual environment. Relevant to the present study, there are researchers who study pediatric speech perception for hearing-impaired children (Dr. Karen Kirk, Speech and Hearing Science), language development (Dr. Pamela Hadley, Speech and Hearing Science),

infant cognition (Dr. Renee Baillargeon, Psychology), and language acquisition (Dr. Cynthia Fisher, Psychology). The PI is part of an active auditory neuroscience journal club with regular interaction among researchers across campus (Dr. Fatima Husain, Speech and Hearing Science; Dr. Jont Allen, Engineering; Dr. Dan Llano, Molecular and Cellular Biology). Additionally, the Speech and Hearing Science Department hosts bi-weekly proseminars with both internal and external invited scholars.

A number of mechanisms to support interdisciplinary collaboration exist at UIUC. The Interdisciplinary Health Sciences Institute facilitates the collaboration of researchers in health sciences and technology. CHAD facilitates collaboration within and across colleges, and organizes regular interdisplinary symposiums. The Beckman Institute fosters interdisciplinary work throughout the university, including researchers in physical sciences, computation, engineering, biology, behavioral sciences, cognition, and neuroscience.

## EQUIPMENT

The equipment necessary for the LENA data collection is currently in place in Dr. Monson's laboratory, including 30 LENA recorders with 24-hr, multi-day recording capability, recorder chargers, and the LENA SP software license. The cloud-based LENA software executes the automated classification algorithm, providing tabulation of different sound category durations for daily, hourly, and 5-minute increments for the recording period. The software also includes an advanced data extraction (ADEX) program that provides additional detail on the recording, including calibrated average and peak sound pressure levels, as well as tabulations for subcategories of sounds (*e.g.*, female language, male language, target child vocalizations, non-target child vocalizations). With 30 LENA recorders, we have the capacity to enroll 15 preterm infants and 15 pregnant women concurrently. The auditory exposure data collection period is 8 to 12 weeks, giving us capacity to collect data from at least 60 subjects per group annually (*i.e.*, 15 subjects per quarter per group).

In Dr. Monson's laboratory there are four Apple computer workstations outfitted with dual-core Intel Core i5 processors and software packages for acoustical analysis (MATLAB, Audacity, Praat) and statistical analysis (R). A lab-dedicated, encrypted, password-protected network server managed by the college's Office of Information, Security and Technology currently provides 10.0 terabytes of storage, upgradable to more storage if needed. The laboratory also holds a large 8 ft x 16 ft double-walled sound-treated booth that can be used for audiological testing, and is currently equipped for speech perception testing and psychoacoustics experiments.

The Audiology Clinic has two double-walled sound-treated booths for conducting all standard audiological assessments. The clinic equipment available for this proposal includes a GSI Tympstar V2 and GSI 39 for tympanometry and screening; a Bio-Logic Scout for otoacoustic emissions; a Bio-Logic Navigator Pro and Intelligent Hearing Systems Duet for auditory brainstem responses; a GSI 62 Clearview video otoscope; two GSI 61 audiometers; and Etymotic 3A insert earphones.

OMB Number: 4040-0001
Expiration Date: 10/31/2019

# RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Brian Middle Name Bruce Last Name*: Monson Suffix:

Position/Title*: Assistant Professor
Organization Name*: UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN
Department: Speech and Hearing Science
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number:

E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI Other Project Role Category:

Degree Type: PHD,MS,BS Degree Year: 2011,2006,2003

Attach Biographical Sketch*: File Name: Biosketch_Monson.pdf

Attach Current & Pending Support: File Name:



Tracking Number: GRANT12962231 Funding Opportunity Number: PAR-18-487 . Received Date: 2019-10-28T12:08:58.000-04:00

PROFILE - Senior/Key Person

Prefix: First Name*: Derrick Middle Name Last Name*: Rollo Suffix:

Position/Title*: Physician, Neonatology
Organization Name*: Carle Foundation Hospital
Department:
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number:

E-Mail*: [redacted]

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: D.O. Degree Year: 2006

Attach Biographical Sketch*: File Name: Biosketch_Rollo.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Carolyn Middle Name J Last Name*: Brown Suffix:

Position/Title*: Professor
Organization Name*: University of Iowa
Department:
Division:
Street1*: [redacted]
Street2:
City*:
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: [redacted]

E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: Consultant Other Project Role Category:

Degree Type: PHD,MA,BA Degree Year: 1989,1982,1980

Attach Biographical Sketch*: File Name: Biosketch_Brown.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Sophie Middle Name E. Last Name*: Ambrose Suffix:

Position/Title*: Director, Communication Development Lab
Organization Name*: Boys Town National Research Hospital
Department:
Division:
Street1*: [redacted]
Street2:
City*:
County:
State*:
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number: [redacted]

E-Mail* [redacted]

Credential, e.g., agency login:

Project Role*: Consultant Other Project Role Category:

Degree Type: PHD,MA,BS Degree Year: 2009,2006,2002

Attach Biographical Sketch*: File Name: Biosketch_Ambrose.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Brittney Middle Name Danielle-Baird Last Name*: Reidy Suffix:

Position/Title*: Clinical Assistant Professor
Organization Name*: University of Illinois at Urbana-Champaign
Department:
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*:

Phone Number*: [redacted] Fax Number:

E-Mail*: [redacted]

Credential, e.g., agency login:

Project Role*: Other (Specify) Other Project Role Category: Clinical Pediatric Audiologist

Degree Type: AuD Degree Year: 2012

Attach Biographical Sketch*: File Name: Biosketch_Reidy.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Sa Middle Name Last Name*: Shen Suffix:

Position/Title*: Director of Biostatistical Services
Organization Name*: University of Illinois at Urbana-Champaign
Department:
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number:

E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: Other (Specify) Other Project Role Category: Biostatistician

Degree Type: Ph.D. Degree Year: 1997

Attach Biographical Sketch*: File Name: Biosketch_Shen.pdf

Attach Current & Pending Support: File Name:

OMB No. 0925 0001 and 0925 0002 (Rev. 09/17 Approved Through 03/31/2020)

## BIOGRAPHICAL SKETCH

Prov de the fo ow ng nformat on for the Sen or/key personne and other s gn f cant contr butors.
Fo ow th s format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Brian Bruce Monson

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Utah State University, Logan, UT | B.S. | 08/2003 | Electrical Engineering |
| Brigham Young University, Provo, UT | M.S. | 08/2006 | Physics (Acoustics) |
| University of Arizona, Tucson, AZ | Ph.D. | 08/2011 | Speech, Language, Hearing Science |
| Duke-NUS Graduate Medical School, Singapore | Postdoc | 12/2013 | Neuroscience |
| Brigham & Women's Hospital, Harvard Medical School, Boston, MA | Postdoc | 05/2016 | Pediatric Newborn Medicine |

### A. Personal Statement

I am an auditory neuroscientist and acoustician. I am also the director of the Auditory Neuro Experience Lab at the University of Illinois at Urbana-Champaign, where we seek to understand how auditory experience over ontogeny and phylogeny shapes the human brain. By virtue of my interdisciplinary training, I am well suited to carry out the proposed study on auditory exposures for neonates. I have the expertise to measure and understand the complex differences between the acoustic environments of the womb (where sounds consist largely of maternal vocal, cardiovascular, and digestive sounds transmitted through amniotic fluid) and of the neonatal intensive care unit (NICU; where sounds consist of mechanical and electronic noise, alarms, and often loud conversation transmitted through air). From my years as a researcher at a well-established research hospital, I bring experience measuring NICU acoustics and conducting collaborative, longitudinal, clinical research with NICU infants. My previous theoretical work modeling the role of experience (over phylogeny and ontogeny) in the development of sensory neural circuitry informs my hypotheses of how different auditory exposures could affect brain development. My work in speech perception provides foundational understanding of principles governing typical and atypical neural processing of speech and language.

Due to family care responsibilities, including three childbirths between 2015-2017 and care for a child diagnosed with special needs in 2015, years 2015-2017 were less productive for me.

### B. Positions and Honors

**Positions and Employment**

2002 Audio Engineer, IVIE Technologies, Inc., Lehi, UT
2002-2003 Sound Engineer, Eclipse, Inc., Logan, UT
2003-2006 Research Assistant, Physics Department, Brigham Young University, Provo, UT
2004 Instructor, Physics Department, Brigham Young University, Provo, UT
2005 Noise Control Consultant, Orem City Public Works, UT
2005-2006 Research Consultant, Samuel Fletcher, Provo, UT

| | |
|---|---|
| 2006-2009 | Predoctoral Research Fellow, Speech/Language/Hearing Sciences Department, University of Arizona, Tucson, AZ |
| 2008 | Instructor, Speech/Language/Hearing Sciences Department, University of Arizona, Tucson, AZ |
| 2008 | Visiting Researcher, Speech/Music/Hearing Group, Royal Institute of Technology, Stockholm, Sweden |
| 2009-2011 | Research Associate, National Center for Voice and Speech, University of Utah, Salt Lake City, UT |
| 2011-2013 | Research Fellow, Neuroscience and Behavioral Disorders Department, Duke-NUS Graduate Medical School, Singapore |
| 2013 | Lecturer, Electrical Engineering and Psychology Departments, National University of Singapore, Singapore |
| 2014-2015 | Postdoctoral Research Fellow, Pediatric Newborn Medicine Department, Brigham and Women's Hospital, Boston, MA |
| 2014-2015 | Research Fellow, Department of Radiology, Children's Hospital Boston, Boston, MA |
| 2014-2016 | Research Fellow in Pediatrics, Harvard Medical School, Boston, MA |
| 2015-2017 | Research Scientist, Pediatric Newborn Medicine Department, Brigham and Women's Hospital, Boston, MA |
| 2015-2017 | Affiliate Research Scientist, Department of Radiology, Children's Hospital Boston, Boston, MA |
| 2016-2017 | Instructor in Pediatrics, Harvard Medical School, Boston, MA |
| 2017- | Assistant Professor, Department of Speech and Hearing Science, University of Illinois at Urbana-Champaign, IL |

**Other Experience and Professional Memberships**

Memberships

| | |
|---|---|
| 2000- | Institute of Electrical and Electronics Engineers (IEEE) |
| 2002- | Tau Beta Pi (Engineering Honor Society) |
| 2003- | Acoustical Society of America |
| 2014- | Association for Research in Otolaryngology |

Service

| | |
|---|---|
| 2004-2006 | Member, Acoustical Society of America Student Council |
| 2005 | Founder, BYU Student Chapter, Acoustical Society of America |
| 2005-2006 | Chair, BYU Student Chapter Executive Council, Acoustical Society of America |
| 2005-2007 | Chair, Acoustical Society of America Student Council |
| 2006- | Ad-hoc reviewer: Proceedings of the National Academy of Sciences; Brain; Human Brain Mapping; NeuroImage; Attention, Perception, and Psychophysics; Trends in Hearing; Ear and Hearing; Journal of the Acoustical Society of America; Journal of Speech, Language, and Hearing Research; Journal of Voice; Frontiers in Neuroscience; Frontiers in Psychology |
| 2014-2016 | Member, Governing Board, Harvard Medical Postdoc Association |
| 2014-2016 | Chair, Advocacy Subcommittee, Harvard Medical Postdoc Association |
| 2014 | Member, Organizing Committee, Future of Research Symposium, Boston, MA |
| 2014-2016 | Member, Advocacy Committee, National Postdoc Association |
| 2015- | Member, Education in Acoustics Committee, Acoustical Society of America |
| 2019 | Symposium Co-organizer, Midwinter Meeting, Association for Research in Otolaryngology |

**Honors and Awards**

| | |
|---|---|
| 2000-2003 | Presidential Scholarship (Academic), Utah State University, Logan, UT |
| 2002 | Tau Beta Pi inductee, Utah Gamma Chapter, Logan, UT |
| 2003 | Graduate *Cum Laude* in Electrical Engineering, Utah State University, Logan, UT |
| 2003-2006 | Physics and Astronomy Scholarship (Academic), Brigham Young University, Provo, UT |
| 2004 | Young Presenter Award, Acoustical Society of America |
| 2006 | Conference Travel Award, Society for Education, Music, and Psychology Research |
| 2006 | Research Presentation Award, Graduate Studies, Brigham Young University, Provo, UT |
| 2006-2009 | Fellowship, Center for Science, Medicine, and the Performing Arts, Dept of Speech, Language, and Hearing Sciences, University of Arizona, Tucson, AZ |
| 2007 | Best Student Paper Award (First Prize), Acoustical Society of America |

| | |
|---|---|
| 2009 | Galileo Circle Scholar Award, College of Science, University of Arizona, Tucson, AZ |
| 2009 | Travel Award, Graduate and Professional Student Council, University of Arizona, Tucson, AZ |
| 2010-2011 | National Research Service Award (Individual Predoctoral), NIH, NIDCD (F31DC010533) |
| 2010 | Fellow, Lessons for Success Research Workshop, American Speech-Language-Hearing Association (ASHA) and NIDCD |
| 2010 | Travel Award, Graduate and Professional Student Council, University of Arizona, Tucson, AZ |
| 2012 | Best Student Paper Award (First Prize), Acoustical Society of America |
| 2012 | Young Investigator Travel Award, Acoustical Society of America |
| 2015 | Selected Attendee, Postdoc Leadership Workshop, Harvard Medical School, Boston, MA |
| 2015 | Travel Award, Auditory Development: From Cochlea to Cognition Meeting, Seattle, WA |
| 2016 | Travel Award, Early-career Acousticians Retreat, Acoustical Society of America |
| 2018 | List of Teachers Ranked as Excellent, University of Illinois at Urbana-Champaign, IL |
| 2019 | List of Teachers Ranked as Excellent, University of Illinois at Urbana-Champaign, IL |

**C. Contributions to Science**

1. My recent work has examined the effect of premature birth on human auditory neurodevelopment. Previous work measuring cortical responses suggested that preterm birth is associated with atypical development of auditory cortical processing in infancy, but the responsible neural underpinnings remain unknown. I used diffusion MRI to (1) characterize the maturational timeline of left hemisphere primary and secondary auditory cortex in Heschl's gyrus for preterm infants and (2) assess the effect of prematurity on primary and secondary auditory cortical microstructure in infancy. By comparing with term-born controls, I demonstrated that both gray and white matter located in Heschl's gyrus in preterm infants exhibit significant microstructural changes that are indicative of lower tissue density. Results were consistent with a delay in maturation of primary and nonprimary auditory cortex. Disrupted maturation in infancy was associated with poorer language ability at longitudinal follow-up. Following on this work, I have also conducted studies assessing the differences between the acoustical environments of the NICU and the womb. I found that NICU incubators attenuate sound substantially more than attenuations reported for sounds passing into the intrauterine environment. I have reported the latter findings in conference abstracts and a submitted manuscript that is currently under revision.
    a. Monson BB, Eaton-Rosen Z, Kapur K, Liebenthal E, Brownell A, Smyser CD, Rogers CE, Inder TE, Warfield SK, and Neil JJ (2018) Differential rates of perinatal maturation of human primary and nonprimary auditory cortex. eNeuro, 5(1) e0380-17.2017, 1-12. PMCID: PMC5773280
    b. Monson BB, and Cull M (2019) Average daily speech exposure for fetuses. Journal of the Acoustical Society of America, 145 (3), 1767.
    c. Monson BB (2017) The auditory experience of infants born prematurely. Journal of the Acoustical Society of America, 141 (5), 3694.

2. While cross-sectional MRI studies have shown that very preterm infants exhibit lower gray and white matter volumes in infancy compared to healthy term-born controls, longitudinal data are lacking. In a prospective observational, longitudinal, cohort study that included 220 preterm infants, brain volumes (cortical gray matter, white matter, subcortical gray matter) were measured at the time of discharge from the hospital and age 7 years. My collaborators and I showed that low brain volumes observed in preterm infants were exaggerated at 7 years, suggesting that infants don't show "catch up" brain growth. Low brain volume in infancy was also associated with worse long-term outcomes in IQ, language, and motor functioning. These results indicate that outcome is already largely determined when the preterm infant goes home from the hospital and emphasize the need for optimizing brain development prior to discharge from the NICU. This was the first longitudinal examination of brain growth between infancy and childhood in this population.
    a. Monson BB, Anderson PJ, Matthews L, Neil JJ, Kapur K, Cheong J, Doyle LW, Thompson DK, and Inder TE (2016) Examination of the pattern of growth of cerebral tissue volumes from hospital discharge to early childhood in very preterm infants. JAMA Pediatrics, 170(8), 772-779. PMCID: PMC5773280
    b. Matthews LGF, Inder TE, Pascoe L, Kapur K, Lee KJ, Monson BB, Doyle LW, Thompson DK, and Anderson PJ (2018) Longitudinal preterm cerebellar volume: perinatal and neurodevelopmental outcome associations. Cerebellum, 17(5), 610-627. PMCID: PMC6126980

3. My research in speech perception has focused on the question of how normal-hearing humans perceive very high-frequency sounds that are produced during speech, but that are inaudible to those with high-frequency hearing loss. Current cochlear implants and hearing aids restore auditory information critical to successful communication, allowing the hearing-impaired to function well in society. Nonetheless, users often complain of communication difficulties in noisy situations, suggesting a need to improve the technology. My research has shown that energy at extended high frequencies (> 8 kHz), which is *not* reproduced or represented well by current hearing aids or cochlear implants, contains information useful for making speech more intelligible in challenging listening environments. Our findings suggest accurate representation of high frequencies in communication devices could improve the user's overall experience.
    a. Monson BB, Rock J, Schulz A, Hoffman E, and Buss E (2019) Ecological cocktail party listening reveals the utility of extended high-frequency hearing. Hearing Research, 381, 107773. PMID: 31404807
    b. Vitela, A. D., Monson BB, and Lotto AJ (2015) Phoneme categorization relying solely on high-frequency energy. Journal of the Acoustical Society of America, 137(1), EL65-EL70. PMCID: PMC4272376
    c. Monson BB, Hunter EJ, and Story BH (2012) Horizontal directivity of low- and high-frequency energy in speech and singing. Journal of the Acoustical Society of America, 132(1), 433-441. PMCID: PMC3407162
    d. Monson BB, Lotto AJ, and Ternström S (2011) Detection of high-frequency energy changes in sustained vowels produced by singers. Journal of the Acoustical Society of America, 129(4), 2263-2268. PMCID: PMC5570078

4. A fundamental dilemma in neuroscience is explaining how biological sensory systems that cannot measure the properties that define the physical world nonetheless guide behaviors that are routinely successful. Rather than resorting to explanations in terms of the physical attributes of sensory stimuli, my collaborators and I drew upon principles of phylogenetic and ontogenetic experience with natural sensory stimuli to develop theoretical models that could explain otherwise puzzling phenomena in auditory and visual perception.
    a. Purves D, Monson BB, Sundararajan J, and Wojtach W (2014) How biological vision succeeds in the physical world. Proceedings of the National Academy of Sciences, 111(13), 4750-4755. PMCID: PMC3977276
    b. Morgenstern Y, Rukmini DV, Monson BB, and Purves D (2014) Properties of artificial neurons that report lightness based on accumulated experience with luminance. Frontiers in Computational Neuroscience. 8:134. PMCID: PMC4217489
    c. Monson BB, Han S, and Purves D (2013) Are auditory percepts determined by experience? PLOS One, 8(5): e63728. PMCID: PMC3646789

5. My earliest work addressed the need to improve noise control for small cooling fans found in standard electronic devices (*e.g.*, computers). While prior efforts had demonstrated the feasibility of utilizing active noise control methods for this application, implementing the technique was limited by space limitations imposed by industry standards and trends toward smaller devices. My research demonstrated one possible solution for this problem by using a smaller cooling fan (running at higher speeds) with active noise control electronics imbedded. With this approach, we achieved reduced noise levels comparable to those achieved for larger, quieter fans.
    a. Monson BB, Sommerfeldt SD, and Gee KL (2007) Improving compactness for active noise control of a small axial cooling fan. Noise Control Engineering Journal 55 (4), 397-407.
    b. Monson BB, Sommerfeldt SD (2004) Global active control of tonal noise from small axial cooling fans. INTER-NOISE and NOISE-CON Congress and Conference Proceedings 9, 327-337.

**Complete List of Published Work in MyBibliography:**
http://www.ncbi.nlm.nih.gov/sites/myncbi/brian.monson.1/bibliography/48121627/public/?sort=date&direction=ascending

**D. Research Support**

Ongoing support

| | | |
|---|---|---|
| Center for Health, Aging and Disability Pilot Grant | Brian Monson (PI) | 07/01/18-12/31/19 |

University of Illinois at Urbana-Champaign
Title: Capturing perinatal auditory experience
The goal of this study is to investigate the differences between intrauterine auditory exposures for fetuses and NICU auditory exposures for preterm infants.
Role: PI

OMB No. 0925 0001 and 0925 0002 (Rev. 09/17 Approved Through 03/31/2020)

## BIOGRAPHICAL SKETCH

Prov de the fo ow ng nformat on for the Sen or/key personne and other s gn f cant contr butors.
Fo ow th s format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Derrick Rollo

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Physician, Neonatology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Wartburg College, Waverly, IA | B.A. | 2002 | Biology |
| Des Moines University, Des Moines, IA | D.O. | 2006 | General Medicine |
| University of Illinois College of Medicine, Peoria, IL | Residency | 2007 | Internal Medicine |
| University of Illinois College of Medicine, Peoria, IL | Residency | 2009 | Pediatrics |
| University of Louisville Kosair Children's Hospital, Louisville, KY | Fellowship | 2012 | Neonatology |

**A. Personal Statement**

I have been a practicing pediatric physician for 13 years with a specialty in Neonatology for 10. I have specific interests in neonatal research, neonatal environmental exposures, neonatal nutrition, and extrauterine growth restriction. I will be directly involved with the proposed research by actively recruiting patients, reviewing charts, and making recommendations to Dr. Monson from a clinical practice perspective in regards to the study.

**B. Positions and Honors**

2015-Present Associate Medical Director of Newborn Services, Perinatal Program, Carle Foundation Hospital
2015-Present Co-Director of Level III Perinatal Program, Carle Foundation Hospital
2014-Present Attending Neonatologist, Carle Foundation Hospital
2014-Present Clinical Assistant Professor, University of Illinois, Urbana-Champaign, IL
2012-2014 Attending Neonatologist, Indiana University
2012-2014 Clinical Instructor, Indiana University, Bloomington, IN
2010 NRP Instructor, Project Vietnam, Saigon, Tuy Hoa, Hanoi
2009-2012 Clinical Instructor, University of Louisville, Louisville, KY
2009-2012 Primary Investigator, University of Louisville, Louisville, KY
2008 Camp Counselor, American Diabetes Association, Camp Granada, Illinois
2007-2009 Program Delegate, American Academy of Pediatrics, Illinois
2006-2009 NRP Instructor, University of Illinois, Peoria, Illinois
2003-2004 Teaching Assistant-Physical Diagnosis, Des Moines University, Des Moines, Iowa
2003-2004 Teaching Assistant-Osteopathic Manipulative Medicine, Des Moines University, Des Moines, Iowa
2003 Research Assistant, Iowa State University, Ames, Iowa
2001 Research Assistant, Colorado State University, Fort Collins, Colorado

**Boards/Membership**
American Board of Pediatrics
American Board of Pediatrics, Neonatal-Perinatal Medicine
National Board of Osteopathic Medical Examiners
American Academy of Pediatrics
American Medical Association

**Honors/Awards**
2011 Fellow Research Award

## C. Contributions to Science

1. Blue light phototherapy is the standard of care for neonatal hyperbilirubinemia (jaundice). Although quantitative measurements of blue light exposure are important, current measurement systems have limited applicability outside of laboratories because of an unfavorable set of factors in bulk, weight, cost, and accuracy. In this study, we used optical metrology approaches, optoelectronic designs, and wireless modes of operation to serve as the basis for miniature, low-cost, and battery-free devices for precise dosimetry. Evaluations on human participants captured instantaneous and cumulative exposure for neonates during blue light phototherapy in our neonatal intensive care unit at Carle Foundation Hospital. We also monitored solar UV exposure for adults during outdoor activities, and tracked light illumination for seasonal affective disorder phototherapy. Versatile applications of this dosimetry platform provide means for consumers and medical providers to modulate light exposure across the electromagnetic spectrum in a way that can both reduce risks in the context of excessive exposure and optimize benefits in the context of phototherapy.
   a. Heo SY, Kim J, Gutruf P, Banks A, Wei P, Pielak R, Balooch G, Shi Y, Araki H, **Rollo D**, Gaede C, Patel M, Kwak JW, Peña-Alcántara AE, Lee KT, Yun Y, Robinson JK, Xu S, Rogers JA (2018) Wireless, battery-free, flexible, miniaturized dosimeters monitor exposure to solar radiation and to light for phototherapy. *Science Trans Med* 10 (470):eaau1643. PMCID: PMC6361379

2. Lactoferrin from human milk provides antimicrobial and anti-inflammatory action in the neonatal intestine. Human milk-fed, critically ill neonates often receive previously frozen milk. Freezing is known to have deleterious effects on proteins. The aim of this study was to determine the effect of low temperature storage of human milk on the concentration of lactoferrin. Milk samples were collected and stored for different periods of time and at different temperatures per Centers for Disease Control and Prevention recommendations. Lactoferrin concentrations following freezing were compared with that in fresh human milk. Lactoferrin concentrations in refrigerated milk samples were stable for 5 days. After 3 months at -18 to -20 C, the average decrease was 37%. Following storage for 6 months at -20 °C, lactoferrin decreased to 46%. Five-day refrigeration of human milk does not appreciably decrease lactoferrin levels. Freezing milk for 3 months or more significantly lowers lactoferrin levels. There may be a role for occasionally providing fresh milk to critically ill neonates.
   a. **Rollo DE**, Radmacher PG, Turcu RM, Myers SR, Adamkin DH (2014) Stability of lactoferrin in stored human milk. *J Perinatology* 34(4):284-286. PMID: 24503914

## D. Additional Information: Research Support and/or Scholastic Performance

**Ongoing**

Center for Health, Aging and Disability Pilot Grant — Brian Monson (PI) — 07/01/18-12/31/19
University of Illinois at Urbana-Champaign
Title: Capturing perinatal auditory experience
The goal of this study is to investigate the differences between intrauterine auditory exposures for fetuses and NICU auditory exposures for preterm infants.
Role: Co-Investigator

OMB No. 0925 0001 and 0925 0002 (Rev. 09/17 Approved Through 03/31/2020)

## BIOGRAPHICAL SKETCH

Prov de the fo ow ng nformat on for the Sen or/key personne and other s gn f cant contr butors.
Fo ow th s format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Carolyn J. Brown

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| University of Iowa, Iowa City, IA | B.S. | 05/1980 | Speech & Hearing Science |
| University of Washington, Seattle, WA | M.S. | 12/1982 | Audiology |
| University of Iowa, Iowa City, IA | Ph.D. | 05/1989 | Hearing Science |

### A. Personal Statement

I am a professor at the University of Iowa with joint appointments in the Department of Communication Sciences and Disorders and Otolaryngology. My research explores the intersection between cochlear implants and auditory physiology. Much of our current work is designed to assess the role of the auditory periphery in determining outcome with a cochlear implant and how “objective” or non-behavioral measures of auditory function, evoked using either acoustic or electrical stimulation can be used to inform clinical decision making. I have an active lab, a history of NIH funding and have mentored the research efforts of a number of young investigators. I have experience working in both medical and academic environments. I have worked as a clinical audiologist and I teach the auditory evoked potential coursework in the CSD program at the University of Iowa and recently helped establish a pediatric auditory evoked response training clinic in our department. All of these experiences will, no doubt, prove helpful in my role as consultant for Brian Monson on this novel and interesting proposal. Although I have not had experience with the LENA system, I am very happy to help him refine the auditory brainstem response methods and troubleshoot as needed during the period covered by this grant.

### B. Positions and Honors

Employment History

| | |
|---|---|
| 1989-1991 | Assistant Professor, Dept. Speech and Hearing Science Arizona State University, Tempe, AZ |
| 1991-1996 | Assistant Research Scientist, Dept. Otolaryngology - HNS, University of Iowa, Iowa City, IA |
| 1996-1997 | Associate Research Scientist, Dept. Otolaryngology – HNS, University of Iowa, Iowa City, IA |
| 1997-2006 | Associate Professor, Dept. Communication Sci & Disorders, University of Iowa, Iowa City, IA & Dept. Otolaryngology – HNS, University of Iowa, Iowa City, IA |
| 2006- | Professor, Dept. Communication Sciences & Disorders, University of Iowa, Iowa City, IA and Dept. Otolaryngology – HNS, University of Iowa, Iowa City, IA |

Professional Memberships

American Speech Language and Hearing Association (CCC-A): member since 1981
Iowa Speech Language and Hearing Association: member since 1985
American Auditory Society (AAS): member since 1996
American Cochlear Implant Alliance (ACI Alliance): member since 2013

Editorial Boards, Manuscript and Grant Review Panels

1998 - 1999 Associate editor: Ear and Hearing (1998-1999)
2008 Invited guest editor: Ear and Hearing (2008)
2008 - 2010 Associate editor: Volta Review (2008-2010)
2009 - 2011 Associate editor: American Journal of Audiology (2009-2011)
2011- 2013 Member: Publication Board, American Speech Lang Hearing Assoc (2011-2013).
2014 Ad Hoc member: special study section to review F31 and F32 applications for NIH/NIDCD
2014 Ad Hoc member: sensorimotor integration study section to review R15 applications for NIH
2015 Ad Hoc member: Auditory Study Section to review R01 applications for NIH/NIDCD
2018 Ad Hoc member: P50 Review panel, ZDC1SRB-K

Honors

1999 Best Research Presentation Award, Custom Sound Outcomes Seminar, Sintra, Portugal
1999-2000 Research Advisor, Best Student Research Paper from American Academy of Audiology
2000 Annual Editor's Award for outstanding research article in Ear and Hearing
2009-2011 Invited Member, CLAS Promotion and Tenure Committee, University of Iowa
2011 Marion L. Huit Distinguished Teaching Award, University of Iowa
2015 Keynote Speaker: International Evoked Response Audiometry Study Group, Busan, Korea
2017 Invited Speaker: Conference on Implantable Auditory Prostheses. Lake Tahoe, California
2018 Invited Speaker: Objective Measures in Auditory Implants. Tel Aviv, Israel

**C. Contributions to Science**

My NCBI Bibliography can be found at the following website:

http://www.ncbi.nlm.nih.gov/sites/myncbi/camille.dunn.1/bibliography/49443426/public/?sort=date&direction=ascending

Electrically Evoked Auditory Potentials: Early Studies

My early work focused on describing and refining objective, or more precisely non-behavioral, methods for assessing hearing in cochlear implant users. Paul Abbas and I were one of the first groups to report methods for recording the electrically evoked auditory brainstem response (EABR) but we are, perhaps, best known for a series of papers that grew out of my dissertation and outlined a method for recording compound action potentials from CI users (ECAPs). At the time we published those studies, CI technology was new and outcomes were variable. Many candidates for a CI were either long deafened or had lost their hearing years ago due to meningitis. This electrically evoked response provided much needed way to assess neural integrity and led to the development of neural telemetry systems available on all commercial CI systems on the market today. Examples of some of these foundational studies include:

Brown, C. J., Abbas, P. J., Gantz, B. (1990). Electrically evoked whole-nerve action potentials: data from human cochlear implant users. The Journal of the Acoustical Society of America, 88(3), 1385-91.

Brown, C. J., Abbas, P. J., Borland, J., Bertschy, M. R. (1996). Electrically evoked whole nerve action potentials in Ineraid cochlear implant users: responses to different stimulating electrode configurations and comparison to psychophysical responses. Journal of Speech and Hearing Research, 39(3), 453-67.

Brown, C. J., Abbas, P. J., Borland, J., Bertschy, M. R. (1996). Electrically evoked whole nerve action potentials in Ineraid cochlear implant users: responses to different stimulating electrode configurations and comparison to psychophysical responses. Journal of Speech and Hearing Research, 39(3), 453-67.

Miller, C. A., Abbas, P. J., Brown, C. J. (2000). An improved method of reducing stimulus artifact in the electrically evoked whole-nerve potential. Ear and Hearing, 21(4), 280-90

Electrically Evoked Compound Action Potentials (ECAP) in Research and in Clinical Practice

ECAPs moved quickly from the lab into the clinic once Cochlear Corporation introduced the Nucleus CI24M device. The primary clinical application for these measures was – and continues to be – as a method for programming the speech processor of the CI. Numerous studies were published that described methods for achieving this goal. Ours were among the first and even today are widely referenced. Beyond predicting MAP levels, this neural response also can be used to track changes in hearing over time, measure current spread and/or channel interaction at the level of the cochlea and characterize the response of the auditory periphery to electrical stimulation. Examples of these studies are listed below. In each case, I played a lead role in all phases of the study including design, data collection and analysis of the outcome.

Hughes, M. L., Brown, C. J., Abbas, P. J., Wolaver, A. A., Gervais, J. P. (2000). Comparison of EAP thresholds with MAP levels in the Nucleus 24 cochlear implant: Data from children. Ear and Hearing, 21(2), 164-74.

Brown, C. J., Hughes, M. L., Luk, B., Abbas, P. J., Wolaver, A., Gervais, J. (2000). The relationship between EAP and EABR thresholds and levels used to program the Nucleus 24 speech processor: Data from adults. Ear and Hearing, 21(2), 151-63.

Abbas, P. J., Hughes, M. L., Brown, C. J., Miller, C. A., South, H. (2004). Channel interaction in cochlear implant users evaluated using the electrically evoked compound action potential. *Audiology & Neurotology*, *9*(4), 203-13.

Miller, C. A., Brown, C. J., Abbas, P. J., Chi, S. L. (2008). The clinical application of potentials evoked from the peripheral auditory system. Hearing Research, 242(1-2), 184-97.

Hybrid Cochlear Implant Studies

The studies below focus on results obtained from CI users with residual acoustic hearing in the implanted ear. This is a unique population and our work describes a novel method of assessing cochlear health.

Abbas, P. J., Tejani, V. D., Scheperle, R. A., Brown, C. J. (2017) Using Neural Response Telemetry to Monitor Physiological Responses to Acoustic Stimulation in Hybrid Cochlear Implant Users. *Ear and Hearing*.38, 409-425. PMID: 28085738.

Shearer AE, Eppsteiner, RW, Frees K, Tejani V, Sloan-Heggen CM, Brown C, Abbas P, Dunn C, Hansen MR, Gantz BJ, Smith RJH. (2017). Genetic variants in the peripheral auditory system significantly affect adult cochlear implant performance. *Hear Res.* 348, 138-142. PMID: 28213135

Kim JR, Tejani VD, Abbas PJ, Brown CJ. (2017). Intracochlear Recordings of Acoustically and Electrically Evoked Potentials in Nucleus Hybrid L24 Cochlear Implant Users and their Relationship to Speech Perception. *Front Neurosci*. 19, 216, PMID 28469553.

Scheperle, R. A., Tejani, V., Omtvedt, J., Brown, C. J., Abbas, P. J., Hansen, M. R., Gantz, B. J., Oleson, J., Ozanne, M. (2017) Delayed Changes in Auditory Status in Cochlear Implant Users with Preserved Acoustic Hearing. *Hear Res*, *350*, 45-57.

**D. Additional Information: Research Support and/or Scholastic Performance**

***Ongoing:***

NIH/NIDCD: P50 DC000242 **Bruce Gantz (PI)**
Funded: 2018-2021
Title: Iowa Cochlear Implant Project VII
Role: PI Project 2: Peripheral Electrophysiology Section

*The studies included during this funding period focus on acoustic and electrically evoked responses that we use to characterize processing of sound at the auditory periphery. Our focus is on CI users with residual acoustic hearing in their implanted ear.*

***Completed:***

NIH/NIDCD: P50 DC000242 **Bruce Gantz (PI)**
Funded: 2011-2017
Title: Iowa Cochlear Implant Project VI
Role: Co-PI Project 4: Electrophysiology Section

*The studies included during this funding period focus on further exploration of clinical applications for electrically evoked auditory potentials in cochlear implant recipients. In this proposal the focus is on Hybrid CI users and on developing a protocol for moving this evoked potential tool into clinical practice.*

NIH/NIDCD: R01 DC012082 **Carolyn Brown (PI)**
Funded: 2012 - 2015, no-cost extension granted until 8/31/16
Title: Evoked Potentials & Music Perception: Effects of Hearing Loss and Training
Role: PI (with Kate Gfeller, Co-PI)

*In this study we use cortical evoked potentials to assess how hearing-impaired listeners perceive music, whether or not they benefit from focused training, and whether the gains they receive from such training generalize to perception of speech in noise.*

NIH/NIDCD: F31 DC012961 **Benjamin Kirby (PI)**
Funded: 2012-2014
Title: The Impact of Frequency Compression on Cortical Evoked Potentials and Perception
Role: Primary Sponsor

*The focus of this proposal is to examine the extent to which cortical evoked potentials might be used as an objective index of the benefits of frequency compression technology on perception.*

NIH/NIDCD: RC1 DC010696 **Carolyn Brown (PI)**
Funded 2009-2012
Title: Optimizing Acoustic and Electric Hearing for Hybrid CI Users
Role: PI (Christopher Turner, Co-PI)

*The goal of this study was to determine how best to divide the acoustic spectrum between the hearing aid and the processor of the cochlear implant for Hybrid CI users. Within-subject comparisons between results obtained using evoked potential and behavioral techniques were compared.*

OMB No. 0925 0001 and 0925 0002 (Rev. 09/17 Approved Through 03/31/2020)

**BIOGRAPHICAL SKETCH**

Prov de the fo ow ng nformat on for the Sen or/key personne and other s gn f cant contr butors.
Fo ow th s format for each person. **DO NOT EXCEED FIVE PAGES**.

NAME: Ambrose, Sophie E.

eRA COMMONS USER NAME (agency login): [redacted]

POSITION TITLE: Coordinator of the Clinical Measurement Program

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| University of Central Arkansas | B.S. | 08/2002 | Speech Language Pathology |
| University of Kansas | M.A. | 08/2006 | Speech Language Pathology |
| University of Kansas | Ph.D. | 12/2009 | Speech Language Pathology |
| Father Flanagan's Boys' Home d/b/a Boys Town Nat'l Research Hospital | Postdoc Fellow | 02/2013 | Communication Disorders |

## A. Personal Statement

I will serve as a consultant on the proposed project, which I think has strong potential to produce findings that help us understand the extent to which the speech, language, and auditory deficits evidenced by infants who spent time in the NICU are a result of experiencing abnormal perinatal auditory input. I will consult with the PI on scientific issues pertaining to the LENA (Language Environment Analysis) recordings and measuring infant vocal development. As one of the earliest adopters of LENA technology, I was able to build collaborations with the LENA Foundation staff, which has allowed me to develop unique expertise pertaining to use of the LENA and has led to presentations and publications on our shared work. Additionally, I have used the technology to pursue my own line of research, which has focused on understanding how the environments of children with hearing loss contribute to variance in their speech, language, and literacy outcomes. Another line of my research has focused on measuring the vocal development of infants and toddlers. This work has included being a co-developer of the Vocal Development Landmarks Interview, a parent-interview tool utilized to measure the vocal development of 6- to 21-month-old infants. Both lines of work have resulted in several publications.

1. **Ambrose, S. E.**, Walker, E., Unflat-Berry, L., Oleson, J., & Moeller, M. P. (2015). Quantity and quality of caregivers' linguistic input to 18-month and 3-year old children who are hard of hearing. *Ear and Hearing*, *36*(*Suppl.* 1)*,* 48–59. **[PMCID: PMC4703365]**

2. VanDam, M., Oller, D. K., **Ambrose, S. E.**, Gray, S., Richards, J. A., Xu, D., . . . Moeller, M. P. (2015). Automated vocal analysis of children with hearing loss and their typical and atypical peers. *Ear and Hearing, 36*(4), 146-152. **[PMCID: PMC4478108]**

3. **Ambrose, S. E.**, Thomas, A., & Moeller, M. P. (2016). Assessing vocal development in infants and toddlers who are hard of hearing: A parent-report tool. Journal of Deaf Studies and Deaf Education, *21*(3), 237-248. **[PMCID: PMC4902879]**

4. Moeller, M. P., Thomas, A. E., Oleson, J., & **Ambrose, S. E.** (2019). Validation of a parent report tool for monitoring early vocal stages in infants. *Journal of Speech, Language, and Hearing Research, 62*(7), 2245-2257. **[PMCID: PMC31265353]**

## B. Positions and Honors

## Positions and Employment

| | |
|---|---|
| 2004-2006 | Research Assistant, Language Intervention Laboratory, University of Kansas Medical Center, Kansas City, KS |
| 2006-2010 | Research Associate and Speech Language Pathologist, Children's Auditory Research and Evaluation Center, House Ear Institute, Los Angeles, CA |
| 2010-2013 | Postdoctoral Fellow, Center for Childhood Deafness, Father Flanagan's Boys' Home doing business as Boys Town National Research Hospital, Omaha, NE |
| 2013-2019 | Staff Scientist and Director of the Communication Development Lab, Center for Childhood Deafness, Language, and Learning, Father Flanagan's Boys' Home doing business as Boys Town National Research Hospital, Omaha, NE |
| 2018- | Coordinator of the Clinical Measurement Program, Center for Childhood Deafness, Language, and Learning, Father Flanagan's Boys' Home doing business as Boys Town National Research Hospital, Omaha, NE |

## Other Experience and Professional Memberships

| | |
|---|---|
| Multiple | **Ad hoc reviewer**: American Journal of Speech-Language Pathology; Ear and Hearing; Folia Phoniatrica et Logopaedica; International Journal of Audiology; Journal of Child Language; Journal of Educational Audiology; Journal of Speech, Language, and Hearing Research; Language Learning and Development; Language, Speech, and Hearing Services in Schools; Perspectives on Hearing and Hearing Disorders in Children; The Volta Review |
| 2006- | Member, American Speech-Language-Hearing Association |
| 2007- | Certificate of Clinical Competence in Speech-Language-Pathology, American Speech-Language-Hearing Association |
| 2010- | License to practice speech-language pathology, State of Nebraska |
| 2011- | Member, International Society for Gesture Studies |
| 2011-2017 | Convention Planning Committee, American Speech-Speech-Language-Hearing Association |
| 2012-2013 | Board member, Hand and Voices |
| 2014-2017 | Professional Development Committee, ASHA Special Interest Group 9 - Hearing and Hearing Disorders in Childhood |
| 2016 | It Takes Two to Talk certification, Hanen Centre |
| 2017- | Hands & Voices Family Leadership in Language and Learning Scientific Language and Literacy Advisory Board |

## Honors

| | |
|---|---|
| 2002 | Lila and Madison Self Graduate Fellow for Master's and Doctoral Studies, University of Kansas |
| 2008 | Convention Recognition, American Speech-Language-Hearing Association |
| 2008 | New Century Doctoral Scholarship, American Speech-Language-Hearing Association Foundation |
| 2009 | Cochlear Implant Trainee Scholarship, 12th Symposium on Cochlear Implants in Children |
| 2010 | Lessons for Success: Emerging Scientists Conference, American Speech-Language-Hearing Association |
| 2011 | Clinical Practice Research Institute, American Speech-Language-Hearing Association |
| 2011 | Research Mentoring Pair Travel Award, American Speech-Language-Hearing Association |
| 2011 | Meritorious Poster, American Speech-Language-Hearing Association Convention |
| 2011 | Student Travel Award, Symposium on Research in Child Language Disorders |
| 2012 | Student Travel Award, Symposium on Research in Child Language Disorders |
| 2015 | Co-recipient of the 2015 Ear and Hearing Editors' Special Recognition for Outcomes of Children with Hearing Loss Special Issue |

## C. Contribution to Science

**1. Characterizing the language and literacy outcomes of children with hearing loss.** Over the past 15 years, the landscape for children with hearing loss has changed dramatically as a result of universal newborn hearing screenings and advances in assistive listening technologies, including cochlear implants. To determine the needs of this new generation of children with hearing loss, it has been necessary to conduct research on their language and literacy outcomes. My dissertation work and my early collaborations with Dr. Jean DesJardin, a collaborator at the House Ear Institute, focused on the literacy skills of preschool and school-age children with cochlear implants. This work established that although the majority of children with cochlear implants were able to establish age-appropriate print knowledge and word reading, they lagged behind their hearing peers in the development of phonological awareness. I continued this line of research as a member of the OCHL investigative team, where our findings indicated that speech production and morphosyntax are particularly vulnerable to the effects of hearing loss. This also fits with the findings I recently published from my R03, which indicate that the gestural abilities of toddlers with hearing loss are intact, but their spoken language skills are delayed in comparison to children with normal hearing. The common theme in the findings of these bodies of research are that children with hearing loss struggle with aspects of language development that are highly dependent upon access to the phonetic details of the speech signal. This work has led to calls for careful monitoring of skill development in areas that may be most impacted by limited auditory access. However, few measures exist that assess skills impacted by auditory access during infancy, thus I recently collaborated with colleagues to develop an innovative new measure of the vocal development of infants and toddlers with hearing loss – the Vocal Development Landmarks Interview.

a. DesJardin, J. L., **Ambrose, S. E.**, & Eisenberg, L. S. (2009). Literacy skills in children with cochlear implants: The importance of early oral language and joint storybook reading. *Journal of Deaf Studies and Deaf Education*, *14*, 22-43. **[PMCID: PMC2605187]**

b. **Ambrose, S. E.**, Fey, M. E., & Eisenberg, L. S. (2012). Phonological awareness and print knowledge of preschool children with cochlear implants. *Journal of Speech, Language, and Hearing Research*, *55*, 811-823. **[PMCID: PMC3370130]**

c. Tomblin, J. B., Harrison, M., **Ambrose, S. E.,** Oleson, J., & Moeller, M. P. (2015). Language outcomes in young children with mild to severe hearing loss. *Ear and Hearing*, *36*(*Suppl.* 1), 76–91. **[PMCID: PMC4704115]**

d. Moeller, M. P., Thomas, A. E., Oleson, J., & **Ambrose, S. E.** (2019). Validation of a parent report tool for monitoring early vocal stages in infants. *Journal of Speech, Language, and Hearing Research, 62*(7), 2245-2257. **[PMCID: PMC31265353]**

**2. Characterizing caregivers' input and the auditory environments of children with hearing loss through use of LENA technology and behavioral observations.** Extensive research has characterized caregiver input within caregiver-child interactions in which the child has normal hearing. Additionally, this line of research has identified the contributions of caregiver input to shaping children's linguistic, academic, and cognitive outcomes. However, the vast majority of research on caregiver-child interactions in which the child has hearing loss was conducted prior to the implementation of universal newborn hearing screenings and recent advances in hearing assistive technologies. Thus, I have sought to characterize the quantity and quality of linguistic input caregivers provide to the current generation of children with hearing loss and how this is influenced by the children's auditory environments. In my collaborations with Dr. Jean DesJardin, we identified aspects of the home literacy environment and higher-level facilitative language techniques utilized by mothers during book reading that are predictive of later language outcomes for children with cochlear implants. In work with the OCHL team utilizing Language Environment Analysis (LENA) technology, my research found that, in comparison to caregivers of children with normal hearing, caregivers of children with hearing loss engaged their children in fewer conversational turns. Conversational turns were decreased in households with high rates of electronic media exposure, pointing toward the importance of children's auditory environments. In other work with the OCHL team, I found that caregivers of children with hearing loss utilized more directive language than caregivers of children with normal hearing. Additionally, in a recent study conducted in my lab, I found that mothers of toddlers with hearing loss are less responsive to their children's gestures than are mothers of toddlers with normal hearing. This work has informed our understanding of how hearing loss can alter caregiver-child interactions, typically in ways that decrease features of input that are known to be facilitative of language development.

a. DesJardin, J. L., **Ambrose, S. E.**, & Eisenberg, L. S. (2011). Maternal involvement in the home literacy environment: Supporting literacy skills in children with cochlear implants. *Communication Disorders Quarterly*, *32*, 135-150. **[Public Access Compliance – N/A, not NIH-funded research]**

b. VanDam, M., **Ambrose, S.E.**, & Moeller, M. P. (2012). Quantity of parental language in the home environments of hard-of-hearing 2-year-olds. *Journal of Deaf Studies and Deaf Education*, *17*, 402-420. **[PMCID: PMC3529623]**

c. **Ambrose, S. E.**, Vandam, M., & Moeller, M. P. (2014). Linguistic input, electronic media, and communication outcomes of toddlers with hearing loss. *Ear and Hearing*, *35*, 139-47. **[PMCID: PMC3944057]**

d. **Ambrose, S. E.** (2016). Gesture use in 14-month-old toddlers with hearing loss and their mothers' responses. *American Journal of Speech-Language-Pathology 25*(4), 519-531. **[PMID: PMC5373693]**

**3. Contributors to variance in speech, language, and literacy outcomes of children with hearing loss.** One of the hallmarks of communication development for children with hearing loss is the high rates of variability in communication outcomes, with some children struggling to develop speech, language, and literacy skills while others develop communication skills on par with those of their hearing peers. My research program has sought to identify sources of variability in children's outcomes. My early work with Dr. Eisenberg, as well as my dissertation work, focused on the contributions of speech perception abilities to language and literacy outcomes. More recently, as a part of the OCHL team, I have explored the contributions of auditory variables to speech and language development, including age at hearing aid fit, degree of hearing loss, audibility, and the benefits provided by hearing aids. I am continuing this work as a co-investigator on the school-age extension of this study (Outcomes of School-Age Children who are Hard of Hearing). The key findings from this work indicate that to promote strong language outcomes for children who are hard of hearing, access to linguistic input via hearing aids must be optimized. Additionally, in the OCHL study, collaborations with Dr. DesJardin, and work in my own laboratory, I have explored the contributions of caregivers' linguistic input to the outcomes of children with hearing loss, identifying specific linguistic behaviors that support children's language development. These findings have informed our understanding of how consistent hearing aid use and high-quality linguistic input can moderate the risk presented by hearing loss to language development.

a. Tomblin, J. B., Oleson, J. J., **Ambrose, S. E.**, Walker, E., & Moeller, M. P. (2014). The influence of hearing aids on the speech and language development of children with hearing loss. *JAMA Otolaryngology – Head & Neck Surgery*, *140*, 403-409. **[PMCID: PMC4066968]**

b. Walker, E., **Ambrose, S. E.,** Oleson, J., & Moeller, M.P. (2017). False belief development in children who are hard of hearing compared to peers with normal hearing. *Journal of Speech, Language, Hearing Research, 60*(12), 3487-3506. **[PMCID: PMC5962924]**

c. **Ambrose, S. E.**, Unflat-Berry, L., Walker, E. A., Harrison, M., Oleson, J. J. & Moeller, M. P. (2014). Speech sound production in 2-year-olds who are hard of hearing. *American Journal of Speech-Language Pathology*, *23*, 91-104. **[PMCID: PMC4035418]**

d. Tomblin, J. B., Oleson, J. J., **Ambrose, S. E.**, Walker, E., & Moeller, M. P. (2018). Early literacy predictors and second-grade outcomes in children who are hard of hearing. *Child Development.* doi: 10.1111/cdev.13158 . **[PMCID: PMC6456443, available 2020-04-09]**

**Complete List of Published Work in MyBibliography:**
**http://www.ncbi.nlm.nih.gov/sites/myncbi/sophie.ambrose.1/bibliography/41280872/public/?sort=date&direction=descending**

## D. Research Support

**Ongoing Research Support**

None

**Completed Research Support**

5 P20 GM109023-04 Leibold (PD) 05/15/14-03/31/19
NIH-NIGMS
***Center for Perception and Communication in Children (CPCC)*** - The goal of the CPCC, a COBRE at the Boys Town National Research Hospital in Omaha, Nebraska, is to expand the range of the current research program by providing a unique environment for the development of junior faculty who have an interest in understanding the consequences of childhood hearing loss for speech and language perception and processing, and ultimately describing performance of children with hearing loss in the real world.
***Project 6: Efficacy of an Early Intervention Addressing Needs of Children with Hearing Loss.*** The long-term objective of this program of research is to develop evidence-based intervention techniques that can be utilized by practitioners to reduce the risk presented by hearing loss to children's language development.
Role: Lead Investigator, Project 6 (Project terminated on 8/1/2018)

5 R01 DC009560-10 Tomblin & Moeller (MPI) 08/01/13-07/31/19 ***(no-cost ext.)***
NIH-NIDCD
***Outcomes of School-Age Children Who are Hard of Hearing***
This project seeks to obtain critical information regarding the language and academic outcomes of a large group of children with mild to severe hearing loss in the school years.
Role: Co-Investigator

5 R03 DC012647-03 Ambrose (PI) 03/04/13-02/28/17 ***(no-cost ext.)***
NIH-NIDCD
***Contributions of Gesture to the Linguistic Outcomes of Children with Hearing Loss***
The overarching goal of this research program is to elucidate the relationships between gesture and spoken language for children with hearing loss.
Role: Principal Investigator

OMB No. 0925 0001 and 0925 0002 (Rev. 09/17 Approved Through 03/31/2020)

## BIOGRAPHICAL SKETCH

Prov de the fo ow ng nformat on for the Sen or/key personne and other s gn f cant contr butors.
Fo ow th s format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Brittney Danielle-Baird Reidy

eRA COMMONS USER NAME (credential, e.g., agency login): n/a

POSITION TITLE: Clinical Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Illinois State University, Normal, IL | B.S. | 12/2001 | Speech Pathology/Audiology |
| Illinois State University, Normal, IL | M.S. | 12/2005 | Audiology |
| AT Still University, Mesa, AZ | AuD | 03/2012 | Audiology |

### A. Personal Statement

Over the course of my 14-year career, I've worked with patients of all ages performing a wide range of audiological assessments, including diagnostic testing, newborn hearing evaluations, electrophysiological testing, dispensing hearing aids and bone-anchored hearing aids, programming cochlear implants, and working with patients with special needs. My specialties include pediatrics, specifically conducting diagnostic auditory brainstem response evaluations on premature and term newborns and children. During my time at Southern Illinois University School of Medicine, I was involved in numerous clinical research projects, in which I conducted pre- and post-treatment clinical assessments for several hundred research subjects. Currently, I am a Clinical Assistant Professor and Audiology Clinic Coordinator at the University of Illinois at Urbana-Champaign. I have performed countless auditory brainstem response evaluations, analyses, and diagnoses on NICU babies, newborns, infants and toddlers, making me well suited to collect the audiological data for this proposal. My role in this study will be primarily to conduct and interpret pediatric audiological assessments, including otoscopy, immittance testing, distortion-product otoacoustic emissions, and diagnostic auditory brainstem responses.

### B. Positions and Honors

**Positions and Employment**

| | |
|---|---|
| 2005 | Audiologist, St. Joseph's Institute for the Deaf, Chesterfield, MO |
| 2006 | Chief Audiologist, Viers Hearing Center, Kirkwood, MO |
| 2006 | Audiologist, Center for Hearing and Speech, St. Louis, MO |
| 2007-2017 | Pediatric Audiologist, Southern Illinois University School of Medicine, Springfield, IL |
| 2018- | Clinical Assistant Professor, Audiology Clinic Coordinator, Department of Speech and Hearing Science, University of Illinois at Urbana-Champaign, IL |

**C. Contributions to Science**

My contributions to science consist largely of collecting audiological data as a Sub Investigator on multiple clinical research projects. Because these were typically industry-sponsored projects assessing the efficacy and safety of different industry-developed drugs or treatments (see below), research products (abstracts, posters, and/or publications) and my role in research product development were limited. Most recently I have been collecting natural sleep auditory brainstem response data on 3-month-old infants for a sponsored project with Dr. Monson as PI.

**D. Additional Information: Research Support and/or Scholastic Performance**

**Ongoing**
Title: Capturing perinatal auditory experience
Sponsor: Center for Health, Aging, and Disability; University of Illinois at Urbana-Champaign
The goal of this study is to investigate the differences between intrauterine auditory exposures for fetuses and NICU auditory exposures for preterm infants.
PI: Monson
Role: Audiologist
July 2018-present

**Completed** (past three years)
Title: A 6-Month, Multicenter, Phase 3, Open-Label Extension Safety Study Of OTO-104 given at 3-Month Intervals by Intratympanic Injection in Subjects with Unilateral Meniere's Disease
Sponsor: Otonomy, Inc
Protocol: 104-201509
The goal of this study was to assess whether multiple injections of an industry-developed drug had any negative impact on hearing, tinnitus, and/or vestibular function for patients with Meniere's disease.
PI: Bauer
Role: Sub Investigator
July 2016 – July 2017

Title: A Prospective, Randomized, Double Blind, Placebo-Controlled, Multicenter, Phase 3 Efficacy and Safety Study of OTO-104 Given as a Single Intratympanic Injection in Subjects with Unilateral Meniere's Disease
Sponsor: Otonomy, Inc
Protocol: 104-201506
The goal of this study was to assess whether a single injection of an industry-developed drug led to improvements in hearing, tinnitus, and/or vestibular function for patients with Meniere's disease.
PI: Bauer
Role: Sub Investigator
May 2016 – May 2017

Title: Safety and Efficacy of EXE844 Otic Suspension in the Treatment of Otitis Media at Time of Tympanostomy Tube Insertion
Sponsor: Alcon
Protocol: EXE844b-C002
The goal of this study was to assess whether an industry-developed ear drop, administered simultaneous with tympanostomy, led to accelerated healing of otitis media for pediatric patients.
PI: Ettema
Role: Sub Investigator
December 2015 – September 2016

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Sa Shen, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Director of Biostatistical Services/Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Sun Yat-sen University, P.R. of China | B.A. | 06/1989 | Mathematics |
| Sun Yat-sen University, P.R. of China | M.S. | 06/1992 | Mathematics |
| University of Pittsburgh, Pittsburgh, PA | Ph.D. | 12/1997 | Statistics |

### A. Personal Statement

As a biostatistician, I have a strong background in academic training and research methodology in statistics, and extensive experience in the application of statistical models in public health research. My research contributions have covered a wide range of fields such as psychiatry, psychology, pediatrics, kinesiology and epidemiology. I am familiar with randomized controlled trials, longitudinal data analyses and statistical genetic analysis, given my previous work with several NIMH or NIH-funded grants. My research at Columbia University and the University of Pittsburgh focused on the application of highly sophisticated statistical approaches for various measurements with a pediatric population. I have conducted statistical analyses identifying psychological and biological antecedents of alcoholism in a longitudinal high-risk offspring design. At the University of Illinois at Urbana-Champaign, I advanced my research on the risk factors for community health problems in people of all ages. I have published many articles on longitudinal studies and randomized clinical trials in peer-reviewed journals. Taken in its entirety, my previous experience as a statistician and co-investigator has given me an extensive background in both design and analysis, which is necessary in my role as the co-investigator/senior biostatistician for the proposed study. With my expertise in these areas, I will work with principal investigator and other co-investigators in the study design, data analysis, and interpretation of the study findings.

### B. Positions and Honors

| | |
|---|---|
| 2013 - present | Associate Professor, Department of Kinesiology and Community Health, College of Applied Health Sciences, University of Illinois at Urbana-Champaign, IL |
| 2013 - present | Director of Biostatistical Services, Center on Health, Aging, and Disability, College of Applied Health Sciences, University of Illinois at Urbana-Champaign, IL |
| 2013 - present | Core Biostatistician, Interdisciplinary Health Sciences Institute, University of Illinois at Urbana-Champaign, IL |
| 2014 - 2015 | Instructor, College of Medicine, University of Illinois at Urbana-Champaign, IL. Course taught: *Medical Statistics*. |
| 2014 - 2015 | Instructor, Department of Kinesiology & Community Health, College of Applied Health Sciences, University of Illinois at Urbana-Champaign, IL. Course taught: *Biostatistics in Public Health*. |
| 2004 - 2013 | Assistant Professor, Department of Psychiatry, Columbia University, New York, NY |

| | |
|---|---|
| 2004 - 2013 | Senior Biostatistician, Research Foundation for Mental Hygiene, New York, NY |
| 2004 - 2013 | Senior Biostatistician, New York State Psychiatric Institute, New York, NY |
| 1997 - 2004 | Senior Statistician, Department of Psychiatry/Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA |

## C. Contributions to Science

1. Longitudinal Data Analysis: I have been interested in analyzing longitudinal health data in adolescents and adults. Specifically, I have applied advanced statistical methods, including generalized estimating equation approaches and generalized linear mixed models, to health outcomes. This includes outcomes from multidisciplinary fields like psychiatry, psychology, pediatrics, and epidemiology and community health.

    a. Bird H.R., Shrout P.E., Duarte C.S., Shen S., Bauermeister J.J., and Canino G. (2008): Longitudinal Mental Health Service and Medication Use for ADHD among Puerto Rican Youth in Two Contexts. Journal of the American Academy of Child and Adolescent Psychiatry, 47(8): 879-889.
    b. Suglia S.F., Shen S., Cohall A., Bird H., Canino G., Brown J., and Duarte C.S. (2016): Use of Health Services by Maltreated Children in Two Different Sociocultural Contexts: Where Can Doors for Interventions Be Opened? Journal of Interpersonal Violence. 2016 Jul 31.
    c. Duarte, C., Eisenberg, R, Musa, G.J., Addolorato, A., Shen, S. and Hoven, C.W. (2017). Children's Knowledge about Parental Exposure to Trauma. Journal of Child & Adolescent Trauma. 10.1007/s40653-017-0159-7.
    d. Geronazzo-Alman L., Eisenberg R., Shen S., Duarte C.S., Musa G.J., Wicks J., Fan B., Doan T., Guffanti G., Bresnahan M., and Hoven C.W. (2017): Cumulative Exposure to work-related traumatic events and current post-traumatic stress disorder in New York City's first responders. Comprehensive Psychiatry, 74:134-143.
    e. An R., Nickols-Richardson S., Alston R., Shen S., and Clarke C. (2019). Fresh and Lean Beef Consumption in Relation to Nutrient Intakes and Diet Quality among U.S. Adults, 2005–2016. *Nutrients*, 11(3), 563; doi: 10.3390/nu11030563.

2. Randomized Controlled Trials: My interest in studying randomized controlled trials began when I worked on a multisite clinical trial with faculty from psychiatry. Since then, I have been collaborating with investigators from various institutes on multiple randomized trials, which are supported by the NIH and NIMH. We have applied the intent-to-treat principle to numerous randomized trials, and examined the effects of treatments and behavioral interventions on health outcomes over time.

    a. Brent D., Greenhill L.L, Compton S., Emslie G., Wells K., Walkup J.T., Vitiello B., Bukstein O., Stanley B., Posner K., Kennard B.D., Coffey B., Cwik M.F., Wagner A., March J.S., Riddle M., Goldstein T., Curry J., Barnett S., Capasso L., Zelazny J., Hughes J., Shen S., Gugga S.S., & Turner J.K., (2009). The Treatment of Adolescent Suicide Attempters (TASA): Predictors of suicidal events in an open treatment trial. Journal of the American Academy of Child and Adolescent Psychiatry, 48(10): 987-996.
    b. Vitiello B., Brent D., Greenhill L.L, Emslie G., Wells K., Walkup J.T., Stanley B., Bukstein O., Kennard B.D., Compton S., Coffey B., Cwik M.F., Posner K., Wagner A., March J.S., Riddle M., Goldstein T., Curry J., Capasso L., Mayes T., Shen S., Gugga S.S., Turner J.K., Barnett S., & Zelazny J. (2009). Depressive symptoms and clinical status during the Treatment of Adolescent Suicide Attempters (TASA) study. Journal of the American Academy of Child and Adolescent Psychiatry, 48(10): 997-1004.
    c. Rynn M.A., Walkup J.T., Compton S.N., Sakolsky D.J., Sherrill J.T., Shen S., Kendall P.C., McCracken J., Albano A.M., Piacentini J., Riddle M.A., Keeton C., Waslick B., Chrisman A., Iyengar S., March J.S., and Birmaher B. (2015): Child/Adolescent Anxiety Multimodal Study: Evaluating Safety. Journal of the American Academy of Child and Adolescent Psychiatry, 54(3): 180-190.
    d. Sung J.H., Shen S., Motl R.W., and Sosnoff J.J. (2016): Bladder Function and Falls in Individuals with MS. *Disability and Rehabilitation.* 38(22): 2193-2197.
    e. Ehlers, D.K., Banducci, S.E., Daugherty, A.M., Fanning, J., Awick, E.A., Porter, G.C., Burzynska, A., Shen, S., Kramer, A.F., and McAuley, E. (2017). Effects of Gait Self-Efficacy and Lower-Extremity

Physical Function on Dual-Task Performance in Older Adults. *BioMedical Research International*. 2017:8570960. doi:10.1155/2017/8570960.

3. Psychometric Assessment: As a senior biostatistician on projects, I also provide collaboration on survey or instrument development and validation.
   a. Posner K., Brown G.K., Stanley B., Brent D.A., Yershova K.V., Oquendo M.A., Currier G.W., Melvin G.A., Greenhill L., Shen S., and Mann J.J. (2011): The Columbia-Suicide Severity Rating Scales: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. American Journal of Psychiatry, 168: 1266-1277.
   b. Matte B., Rohde L.A., Turner B., Fisher P.W., Shen S., and Bau C.H.D. (2015): Reliability and Validity of Proposed DSM-5 ADHD Symptoms in a Clinical Sample of Adults. The Journal of Neuropsychiatry and Clinical Neurosciences, 27(3): 228-236.
   c. Sung J., Ousley C.M., Shen S., Isaacs Z.J., Sosnoff J.J., and Rice L.A. (2016): Reliability and validity of the function in sitting test in nonambulatory individuals with multiple sclerosis. International Journal of Rehabilitation Research. 39(4):308-312.

4. Functional Magnetic Resonance Imaging (fMRI) Analysis: I have applied statistical methods for fMRI data analysis to investigate brain functions so that we can better understand the neurological and psychological changes associated with psychiatric disorders.
   a. Hill S.Y., DeBellis M.D., Keshavan, M.S., Lowers L., Shen S., Hall J., and Pitts T. (2001): Right Amygdala Volume in Adolescent and Young Adult Offspring from Families at High Risk for Developing Alcoholism. Biological Psychiatry, 49: 894-905.

**D. Additional information: Research Support**

Burroughs Wellcome Fund (PI: Kimani Toussaint) 6/1/2017 – 5/31/2021
Investigating the Mechanobiology of Cervical Remodeling Using a Novel Combination of Optical Microscopy and Nanoindentation.
This project is to determine the structural and mechanical properties of cervical tissue as a function of gestational age by using novel imaging and mechanical metrology techniques.
Role: Statistician

RG 1507-05433
National Institute of Health (PI: Jacob Sosnoff) 4/1/2016-3/31/2020
Virtual Reality-treadmill Combined Intervention for Enhancing Mobility and Cognitive Function in Patients with Relapsing-Remitting Multiple Sclerosis
This project examines the efficacy of virtual reality training combined with treadmill training on mobility, cognition and quality of life in persons with multiple sclerosis.
Role: Co-I

R01 AG052707
National Institute of Health (PI: Sean Mullen) 9/1/2016-5/31/2021
Cognitive Regulation Training and Exercise (CORTEX)-II with Middle-aged Adults
This project is to compare CORTEX**,** a multi-faceted, general and exercise-specific cognitive training program (involving 20 hours of active and traditional computerized cognitive training, delivered via a training center and at home) to an attention-control condition involving health and wellness informational videos.
Role: Co-I

RG-1701-26862
National Multiple Sclerosis Society (PI: Laura Rice) 10/1/2017-9/30/2020
Validation of a Fall Prevention Program Among Non-Ambulatory Wheeled Mobility Device Users with Multiple Sclerosis
This project is to examine the efficacy of a community-based rehabilitation educational intervention on management of falls in non-ambulatory individuals with MS (Multifactorial Fall Prevention Program, MFPP).

Role: Co-I

# PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 03/31/2020

## 1. Vertebrate Animals Section

Are vertebrate animals euthanized? ○ Yes ● No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

○ Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

## 2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period *Anticipated Amount ($) *Source(s)

# PHS 398 Cover Page Supplement

## 3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

❑ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

## 4. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ○ Yes ● No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

## 5. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

# PHS 398 Modular Budget

OMB Number: 0925-0001
Expiration Date: 03/31/2020

## Budget Period: 1

Start Date: 07/01/2020 End Date: 06/30/2021

### A. Direct Costs

| | Funds Requested ($) |
|---|---|
| Direct Cost less Consortium Indirect (F&A)* | [redacted] |
| Consortium Indirect (F&A) | [redacted] |
| Total Direct Costs* | [redacted] |

### B. Indirect (F&A) Costs

| | Indirect (F&A) Type | Indirect (F&A) Rate (%) | Indirect (F&A) Base ($) | Funds Requested ($) |
|---|---|---|---|---|
| 1. | MTDC | [redacted] | | [redacted] |
| 2. | | | | |
| 3. | | | | |
| 4. | | | | |

Cognizant Agency (Agency Name, POC Name and Phone Number): Office of Naval Research (ONR) Sharon Gales [redacted]

Indirect (F&A) Rate Agreement Date: 12/21/2017

Total Indirect (F&A) Costs: [redacted]

### C. Total Direct and Indirect (F&A) Costs (A + B)

Funds Requested ($): [redacted]





Funding Opportunity Number: PAR-18-487. Received Date: 2019-10-28T12:08:58.000-04:00

# PHS 398 Modular Budget

Budget Period: 2

Start Date: 07/01/2021 End Date: 06/30/2022

## A. Direct Costs

Funds Requested ($)

Direct Cost less Consortium Indirect (F&A)* [redacted]

Consortium Indirect (F&A)

Total Direct Costs* [redacted]

## B. Indirect (F&A) Costs

| | Indirect (F&A) Type | Indirect (F&A) Rate (%) | Indirect (F&A) Base ($) | Funds Requested ($) |
|---|---|---|---|---|
| 1. | MTDC | [redacted] | | [redacted] |
| 2. | | | | |
| 3. | | | | |
| 4. | | | | |

Cognizant Agency (Agency Name, POC Name and Phone Number) Office of Naval Research (ONR) Sharon Gales [redacted]

Indirect (F&A) Rate Agreement Date 12/21/2017

Total Indirect (F&A) Costs [redacted]

## C. Total Direct and Indirect (F&A) Costs (A + B)

Funds Requested ($) [redacted]





Funding Opportunity Number: PAR-18-487. Received Date: 2019-10-28T12:08:58.000-04:00

# PHS 398 Modular Budget

Budget Period: 3

Start Date: 07/01/2022 End Date: 06/30/2023

## A. Direct Costs

| | Funds Requested ($) |
|---|---|
| Direct Cost less Consortium Indirect (F&A)* | [redacted] |
| Consortium Indirect (F&A) | |
| Total Direct Costs* | [redacted] |

## B. Indirect (F&A) Costs

| | Indirect (F&A) Type | Indirect (F&A) Rate (%) | Indirect (F&A) Base ($) | Funds Requested ($) |
|---|---|---|---|---|
| 1. | MTDC | [redacted] | | [redacted] |
| 2. | | | | |
| 3. | | | | |
| 4. | | | | |

Cognizant Agency (Agency Name, POC Name and Phone Number): Office of Naval Research (ONR) Sharon Gales [redacted]

Indirect (F&A) Rate Agreement Date: 12/21/2017

Total Indirect (F&A) Costs: [redacted]

## C. Total Direct and Indirect (F&A) Costs (A + B)

Funds Requested ($): [redacted]





Funding Opportunity Number: PAR-18-487. Received Date: 2019-10-28T12:08:58.000-04:00

# PHS 398 Modular Budget

## Cumulative Budget Information

### 1. Total Costs, Entire Project Period

| | |
|---|---|
| Section A, Total Direct Cost less Consortium Indirect (F&A) for Entire Project Period ($) | [redacted] |
| Section A, Total Consortium Indirect (F&A) for Entire Project Period ($) | [redacted] |
| Section A, Total Direct Costs for Entire Project Period ($) | [redacted] |
| Section B, Total Indirect (F&A) Costs for Entire Project Period ($) | [redacted] |
| Section C, Total Direct and Indirect (F&A) Costs (A+B) for Entire Project Period ($) | [redacted] |

### 2. Budget Justifications

| | |
|---|---|
| Personnel Justification | Personnel_Justification.pdf |
| Consortium Justification | Consortium_Justification_Carle.pdf |
| Additional Narrative Justification | |





Funding Opportunity Number: PAR-18-487. Received Date: 2019-10-28T12:08:58.000-04:00

## Personnel Justification

**Brian Monson, PhD, Principal Investigator** (5 calendar months effort, salary support requested for 2.85 summer months). Dr. Monson is an Assistant Professor in the Department of Speech & Hearing Science at the University of Illinois at Urbana-Champaign. Dr. Monson will assume primary responsibility and scientific leadership of the proposed project. Dr. Monson's responsibilities will include training and oversight of training research staff for data collection and analysis, and presenting and publishing study findings. Dr. Monson will also assume responsibility for administering parent surveys outlined in the research protocol. Dr. Monson has experience with training and ongoing supervision of research personnel for data collection and analysis, as well as experience in the administration of clinical research for infants born premature. This, along with his expertise in acoustical measurements, neuroscience, and brain development demonstrate his ability to independently contribute and assume full responsibility for the project.

**Derrick Rollo, DO, Co-Investigator** (0.36 calendar months effort). Dr. Rollo is an attending neonatologist at Carle Foundation Hospital with over 13 years of experience as a physician. He also has past research experience and an established collaborative relationship with the PI. Dr. Rollo will provide clinical guidance to the project and also oversee the collection of NICU data proposed in this project. Dr. Rollo will be a key liaison for recruitment of patients in the clinical studies from the hospital floor.

**Carolyn J. Brown, PhD, Consultant** (no salary support requested). Dr. Brown is a Professor in the Department of Speech Pathology and Audiology at the University of Iowa. She is a leading researcher with a long publication list and expertise in auditory evoked potentials and pediatric audiology. Quarterly meetings will be held with Dr. Brown to review progress and discuss audiological data. We are requesting funds for Dr. Brown's consultant fee.

**Sophie E. Ambrose, PhD, Consultant** (no salary support requested). Dr. Ambrose is a Staff Scientist and the Coordinator of the Clinical Measurement Program at Boys Town National Research Hospital. She has expertise in LENA device use and LENA data analysis. She is an expert on infant vocalization and language development and co-developer of the Vocal Development Landmarks Interview parent report tool. Quarterly teleconference meetings will be held with Dr. Ambrose to review progress and discuss LENA data. We are requesting funds for Dr. Ambrose's consultant fee.

**Brittney Reidy, AuD, Clinical Pediatric Audiologist** (2.2 calendar months effort). Dr. Reidy is a Clinical Assistant Professor in the Department of Speech & Hearing Science at the University of Illinois at Urbana-Champaign. Dr. Reidy has expertise in obtaining auditory brainstem responses (ABR) and other audiological data from infants, with over 10 years of pediatric audiology experience. On a weekly basis, Dr. Reidy will conduct and oversee all clinical audiological assessments and ABR data collection for the infants at 3 months of age.

**Sa Shen, PhD, Biostatistician** (0.5 calendar months of salary support in Year 2 and Year 3 are requested). Dr. Shen will provide assistance with data analysis and interpretation for the proposed project. Dr. Shen is the Director of Biostatistics for the Center for Health, Aging and Disability at the University of Illinois at Urbana-Champaign. Critical to the present proposal, Dr. Shen brings expertise in experimental design and analysis of longitudinal data.

**TBD Graduate Research Assistant** (salary support requested for 9 academic months [with tuition remission] and 3 summer months [hourly]). A TBD 30%-time graduate research assistant will be recruited and hired to assist with participant recruitment, participant scheduling, data collection, and data analysis. Tuition remission is assessed at 64% of GRA salaries.

[redacted]

# PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 03/31/2020

| | |
|---|---|
| **Introduction** | |
| 1. Introduction to Application (for Resubmission and Revision applications) | Introduction_to_Application.pdf |
| **Research Plan Section** | |
| 2. Specific Aims | Specific_Aims.pdf |
| 3. Research Strategy* | Research_Strategy.pdf |
| 4. Progress Report Publication List | |
| **Other Research Plan Section** | |
| 5. Vertebrate Animals | |
| 6. Select Agent Research | |
| 7. Multiple PD/PI Leadership Plan | |
| 8. Consortium/Contractual Arrangements | Letter_of_Intent_Carle.pdf |
| 9. Letters of Support | Letters_of_Support.pdf |
| 10. Resource Sharing Plan(s) | Resource_Sharing_Plan.pdf |
| 11. Authentication of Key Biological and/or Chemical Resources | |
| **Appendix** | |
| 12. Appendix | |



Tracking Number: GRANT12962231
Funding Opportunity Number: PAR-18-487. Received Date: 2019-10-28T12:08:58.000-04:00

**Introduction**

| Reviewer | SIG. | INVEST. | INNOV. | APP. | ENV. |
|---|---|---|---|---|---|
| One | 2 | 2 | 2 | 4 | 1 |
| Two | 2 | 2 | 2 | 4 | 2 |
| Three | 3 | 3 | 4 | 4 | 2 |

We appreciate the helpful comments from all three reviewers. For reference, reviewer scores are shown in the table. We have addressed the critiques, as outlined below, resulting in a much stronger proposal. *Sections where revisions were made are indicated throughout by vertical bars in the left margin.*

**SIGNIFICANCE**. **Auditory input vs. other factors**. We agree with Reviewer 3 that it will be challenging to distinguish between effects of auditory input *vs*. other sensory input *vs*. other medical factors (*e.g.*, nutrition) on developmental outcomes. This proposal represents a critical first step to tackling this issue by providing presently unavailable data on NICU auditory input. We will collect many other medical factors. Although capturing comprehensive sensory input is not feasible, we will document infant skin-to-skin time as a somatosensory variable. We will track patients' transition from our NICU's low-lighting unit, to main unit while still in a covered incubator (allowing medium lighting), to main unit in an open crib (regular lighting). We can use these transitions to mark increased luminance and visual input. We will also document the use of blindfolds, which sometimes occurs. We will document nutrition type (mother's breast milk *vs*. donor milk *vs*. formula) and drug administration, which we will use as covariates in our statistical models. We have added these clarifications to our proposal. **Other**. Other critiques raised under *SIGNIFICANCE* were also raised under *APPROACH* and are addressed below.

**INVESTIGATOR**. As suggested, we increased PI effort from 3 months to 5 months. We also added a consultant with additional expertise in LENA data analysis, as well as infant vocal and communication development.

**INNOVATION**. Following suggestions from Reviewers 1 and 2, we modified Aims 1A (removed analysis of noise), 1B (changed to a time-varying analysis of circadian patterns), and 2 (specified tone burst ABRs only) to omit predictable results. We added that, due to our modified approach for Aim 2, we will be collecting normative ABR data at 6 and 8 kHz for infants. There has been a surge of interest in the perceptual value of these high frequencies due to emerging evidence that very high frequencies play a larger role in speech perception than previously believed. Having high frequency data for full-term and preterm infants will be an important contribution.

**APPROACH**. **Preterm infant vocalizations**. We share the reviewers' concerns regarding LENA's accuracy in detecting preterm infant vocalizations. We removed this analysis due to this technological limitation. With Reviewer 1's suggestion to use LENA metrics as covariates for ABRs, and based on new evidence from preliminary data, we modified Aim 3 to assess the relationship between perinatal language exposure and ABR latencies rather than vocalizations. **Aim 2**. We incorporated Reviewer 1's suggestions (changed the ABR protocol to only 2 click levels; added rationale for a potential frequency-dependent vulnerability; prioritized data collection at 6 and 8 kHz; and clarified that we obtain thresholds for infants with no responses at 25 dBnHL). With this approach we have successfully collected preliminary data at all frequencies for 11 of 12 infants. **Intrauterine acoustic environment**. We apologize that we did not adequately convey our considerations on this important topic previously. We now include them. We think the reviewers' comments reflect the commonly held belief that the intrauterine transfer function is a low-pass filter. Although it has been reported that this function approximates a low-pass filter, both human and animal data suggest maximal attenuation at high frequencies is less than 20 dB.[1] [2] The available human data indicate large intersubject variability, with some women's transfer functions exhibiting level ***gains*** for bands up to 2 kHz.[1] Only one subject displayed attenuation >5 dB at all frequency bands from 1 to 8 kHz. Animal and synthetic models reveal that the filter is also highly dependent upon the receiver location.[2] [3] Absolute frequency-band level estimates for the intrauterine noise floor indicate it is dominated by low-frequency (<200 Hz) cardiovascular and digestive sound sources.[4] Thus the common belief that fetuses have no access to spectral information at higher frequencies deserves some reconsideration. There is frequency-dependent maturation of the auditory system[5] and a direct fluid acoustic pathway to the inner ear that will further constrain what the fetus actually *hears*. However, it appears clear that at least voice,[6] pitch,[7] vowel formant,[8] and temporal information are available to and learned by the fetus,[9] and that fetuses can hear at least 3-kHz tones[10] and 5-kHz octave bands[11] at later gestational ages. Given these data and constraints, we believe the safest assumption is that fetuses have access to much spectral information much of the time. Nonetheless, we propose to apply a uterine filter to our recordings based on mean values from humans,[1] and then exclude any audio that falls below the putative uterine noise floor at all frequency bands. **Other**. A comparison of incubator and womb transfer functions is now included as suggested (Fig. 3). We clarified that we will document use of respiratory devices during our recordings. Data labelled "Silence" during use of nasal cannulas will be relabeled as "Noise." We included sex effects in the speech exposure analysis and infant sex as a covariate for our ABR analysis.

**GENERAL.** We recognize that a study of this nature will have some limitations. In spite of these limitations, the Aims of the present proposal will yield subject-specific NICU sound exposure data, typical fetal extrauterine language and sound exposure data, and normative 6- and 8-kHz tone burst infant ABR data, all of which are presently unavailable. We feel that access to these valuable data warrants the proposed efforts.

Being reared in abnormal acoustic environments results in detrimental effects on auditory brain development. Animal studies clearly demonstrate this principle, revealing particularly dire consequences when the abnormal auditory experience occurs during critical periods of neurodevelopment. Perhaps nowhere are these findings more alarmingly relevant for humans than for premature infants in the neonatal intensive care unit (NICU). During a period of rapid auditory and brain development that would ordinarily occur *in utero*, preterm infants are deprived of the intrauterine environment, including the highly unique intrauterine sounds. Relative to the womb, the NICU imposes drastic changes to perinatal auditory input, including high (potentially noxious) sound levels, a change in the transmission medium (air *vs*. fluid), and replacement of constant biological sounds (*e.g.*, mother's voice and heartbeat) with non-biological sounds (*e.g.*, electronic alarms and mechanical noise) and periods of silence. Because humans have precocial hearing, preterm infants are listening to and learning about these surrounding sounds. Medical advances have dramatically improved survival rates for preterm infants, but long-term morbidities, including speech, language and auditory deficits, are widely reported. To what extent are these deficits a result of abnormal perinatal auditory input?

Our understanding of the impact of NICU auditory exposures on human communication development is limited. The need to improve this understanding is urgent; within the United States alone, over 500,000 infants are born premature each year, with most spending time in the NICU. Indeed, the preterm infant is a prime target for NIDCD's stated priorities to (1) "define the underserved population of infants and children for hearing health care" and (2) "develop…new effective interventions and approaches tailored for understudied populations or conditions." In the current proposal, we focus on this underserved population, with the **long-term goal** of developing interventions designed to optimize auditory experience for premature infants.

*Critical barriers* to achieving this long-term goal are (1) the lack of adequate information about the present auditory experience for the premature infant, and (2) the lack of comprehensive data on auditory outcomes for this population. With our team's expertise in newborn medicine, neuroscience, acoustics, pediatric audiology, and communication development, we are uniquely positioned to address these two barriers. We will focus on capturing auditory exposures and medical course for each infant throughout NICU stay. We then propose to evaluate the effects of NICU auditory exposures on infant auditory pathway development. Our approach will be divided into three Specific Aims.

**Aim 1: Determine the difference between intrauterine and NICU auditory exposures for human infants**
Comprehensive auditory experience will be captured for very preterm (VPT) infants and typically developing fetuses using small 24-hr audio recording devices (LENA). For VPT infants, LENA devices will be placed in the incubator or crib to reside with the infant. For fetuses, LENA devices will be worn near the abdomen of the pregnant mother. Recordings will be obtained multiples times per week. Three hypotheses will be tested:

A. Language exposure in the NICU is less than that experienced *in utero*.
B. Language, noise, and other sound exposures follow a circadian pattern for fetuses, but not for VPT infants.
C. Exposure to sounds ≥400 Hz in the NICU increases with time between birth and discharge as VPT infants transition from enclosed infant incubators (less stable condition) to open cribs (more stable condition).

Rationale: These hypotheses derive primarily from observations made with our preliminary data.

**Aim 2: Determine the effect of VPT birth on auditory neurodevelopment**
VPT and full-term (FT) infants will undergo diagnostic auditory brainstem responses (ABR) at 52 weeks postmenstrual age (PMA; *i.e.*, 12 weeks after full term equivalent age). Hypothesis:

A. VPT birth leads to longer latency tone burst ABRs at 52 weeks PMA.

Rationale: Studies have demonstrated auditory pathway maturation is delayed by VPT birth.

**Aim 3: Determine the relationship between perinatal auditory exposures and auditory neurodevelopment**
The relationship between perinatal auditory exposure metrics and auditory brainstem development at 44 weeks and 52 weeks PMA will be assessed. Hypothesis:

A. Greater language exposure during perinatal brain development leads to more rapid auditory neurodevelopment.

Rationale: This hypothesis stems directly from our preliminary data and observations.

Only when we fully understand the relationship between perinatal auditory experience and later communication outcomes will we be able to introduce personalized, effective therapies to optimize that experience and improve outcomes for this fragile population. The proposed Aims are first steps critical to this understanding and will provide a treasure trove of much needed data that will yield important contributions for years to come. Furthermore, the proposed study will lay the foundation for an **R01 proposal** aimed to assess long-term communication and neurodevelopmental outcomes for this cohort of VPT infants during longitudinal follow-up.

**Significance**

Prenatal auditory function. Humans are altricial mammals with precocial hearing. In contrast with many other altricial mammalian species, nature has deemed human prenatal auditory experience of sufficient value to warrant the activation of auditory function as early as 25 weeks postmenstrual age (PMA), some 15 weeks prior to full-term (FT) birth.[10] [12-14] *What are fetuses hearing?*

The prenatal acoustic environment is unique, with the endogenous noise floor dominated by constant low-frequency sources of mother's cardiovascular and digestive sounds transmitted *via* amniotic fluid.[15-17] Also present are the sounds of mother's vocalizations, as well as extrauterine vocalizations, music, and other airborne sounds that impinge on the abdomen of the mother and exceed the endogenous noise floor.[17] [18] The extrauterine airborne sounds are filtered by the extra-to-intrauterine transfer function, which can attenuate higher frequencies more than low frequencies, although maximal attenuation tends to be only ~15 dB observed at 4 kHz, with less attenuation at 8 kHz.[1] [2] The available human data indicate large intersubject variability, with some women's transfer functions exhibiting level *gains* for frequency bands up to 2 kHz.[1] Animal and synthetic model data reveal that the transfer function is also highly dependent upon the receiver location in the uterus.[2] [3] Thus fetuses have access to much spectral information from extrauterine sounds, although which frequency bands are most prominent can depend greatly upon maternal anatomy, sound source location, and fetal head location. Further constraining what fetuses actually *hear* is the direct fluid acoustic pathway to the inner ear, which could bypass typical middle ear function,[9] and the frequency-dependent maturation of auditory sensitivity, which begins during fetal development and continues into childhood.[5] For example, fetuses first demonstrate behavioral responses to extrauterine low-frequency tones (≤500 Hz) around 25 weeks PMA, with responses to 1- and 3-kHz tones developing around 32 weeks PMA.[10] Remarkably, the immature fetal brain possesses capabilities for auditory learning and memory of extrauterine sounds. FT newborns exhibit behavioral and neurophysiological responses that distinguish between acoustic stimuli to which they were exposed *in utero* (*e.g.,* mother's voice) and novel stimuli (*e.g.*, stranger's voice).[6-8] [19-22] Thus it seems clear that at least voice,[6] pitch,[7] vowel formant,[8] and temporal information is available to and learned by the fetus,[9] and is likely more prominent for male than female voices.[18]

Less clear is whether prenatal auditory experience has lasting effects on auditory development or communication behavior. Though there exist reports that loud noise exposures for pregnant mothers are associated with hearing loss in their newborns,[23] [24] these findings have been criticized due to methodological shortcomings.[15] [25] Animal studies have documented hearing loss in fetuses that were exposed prenatally to sound pressure levels (SPL) in excess of 115 dB SPL for extended periods,[26] [27] but such levels and durations are beyond that of typical human exposures. Prenatal hearing and auditory learning is facilitated by a neural pathway mature enough to permit cochlear input to reach at least primary and nonprimary auditory cortical regions.[21] [28] [29] The role of experience generally in shaping this pathway has been well established. Animal models clearly indicate that normal auditory circuit development is dependent on extrinsic auditory stimulation.[30] Thus degradation or deprivation of acoustic information during critical developmental periods has lasting detrimental neural and behavioral consequences.[31] This principle has been demonstrated for early deafness in humans with cochlear implants[32] [33] and in animal models of early deafness,[34] [35] temporary hearing loss,[36] [37] and acoustic enrichment.[38] Normal hearing animals reared in unnatural acoustic environments (*e.g.*, hearing only white noise) exhibit marked abnormalities in auditory cortex.[39] Normal hearing animals deprived of conspecific vocalizations during critical learning periods also exhibit neural abnormalities and communication deficits.[40] Auditory cortex maps in mice are influenced by acoustic input within days after hearing onset.[41] Notably, these studies have largely been conducted following FT birth of the animals, albeit shortly after hearing onset. Here we propose to examine human auditory experience *prior* to FT age.

Preterm birth: clinical significance. If intrauterine auditory experiential benefits warrant prenatal auditory function and learning, *what are the effects of disrupting that auditory experience with preterm birth?*

Nowadays infants born as early as 23-24 weeks' gestation often survive to adulthood with modern medical care. These infants undergo a rapid and premature change in auditory input as they transition to the acoustic environment of the neonatal intensive care unit (NICU). Here they are exposed to high sound levels,[42] unnatural electronic and mechanical noises,[43] and periods of silence,[43] [44] all transmitted *via* air rather than fluid (see the Table). Preterm infants suffer from a high incidence of neurodevelopmental problems,[45] many of which are linked with auditory function. For example, the preterm population has a relatively high incidence of sensorineural hearing loss (approx. 1.5%, compared to 0.1-0.3% for healthy infants)[46-49] and auditory neuropathy,[50] [51] as well as central auditory processing disorder.[52] [53] Even preterm infants with no

| Typical Exposures | Womb | NICU |
|---|---|---|
| Maternal voice | Always | Sometimes |
| Non-maternal voices | Often | Often |
| Heartbeat | Always | Never |
| Silence | Never | Often |
| Alarms | Rarely | Often |
| Biological noise | Always | Never |
| Airborne noise | Sometimes | Often |
| High sound levels | Unknown | Often |
| Medium | Fluid | Air |

diagnosis of auditory pathology exhibit cognitive impairments related to audition, including auditory attention deficits[54] and widely reported speech/language comprehension and production deficits.[55-57] Neural mechanisms underlying these impairments are not clear, although central mechanisms have been implicated since cochlear function measured with otoacoustic emissions (OAEs) appears to be similar between term-born infants and preterm infants at term-equivalent age.[58 59] Auditory brainstem response (ABR) latencies indicate auditory pathway maturation is delayed for preterm infants at term-equivalent age.[60-64] Some have attributed this group difference in ABR latencies to possible conductive loss in the preterm population.[64 65] Differences between cortical evoked potentials for term and preterm infants have also been reported.[65] Perhaps related to abnormal cortical responses, prior work from our lab and others has revealed structural abnormalities in cortical gray and white matter for preterm infants with whole-brain measures[66-68] and in auditory cortex specifically.[69] Additionally, these structural abnormalities in infancy were associated with poorer language abilities later in childhood.[68 69]

Now is an especially critical time to consider preterm infant auditory experience as recent changes to NICU design are altering this experience. Namely, a current trend in hospitals worldwide is to reconstruct open layout, multi-bed NICU designs into private, single-patient rooms.[70] A consequence of this redesign is a substantial change to auditory input for NICU patients, with increased amounts of silence and decreased amounts of language exposure.[43] Given that silence is a condition never experienced *in utero* (owing to the presence of mother's heartbeat and other biological sounds),[17] this change could have consequences for the developing brain. Two reports suggest that acoustic input during NICU stay might have lasting effects on communication skills for preterm infants. One report showed that the amount of exposure to adult speech during NICU stay correlated with language scores at age 7 and 18 months.[71] The other report examined very preterm infants who were randomly assigned to either a noisier open ward multi-bed NICU or a quieter single patient private room.[72] Contrary to the original hypothesis, language scores were poorer for the single patient room group at age 2 years. It was proposed that the quiet conditions led to auditory deprivation. To what extent neurodevelopmental deficits observed for preterm infants can be explained by abnormal auditory exposures, and whether differential effects of auditory input *vs.* other biological and medical factors can be disentangled remain open and challenging questions. This proposal is an essential first step to begin to address these questions.

Experiments outlined in this proposal will be focused on capturing auditory experience during the preterm period. Previous efforts to characterize individual preterm infants' auditory exposures have been limited in two ways: 1) only two[44] or four[43] discrete 16-hr periods were measured to approximate auditory experience during NICU stay (which can last up to four months); 2) no analysis of a typically developing control group was conducted. Here we address these shortcomings by analyzing auditory exposures both for NICU infants *and* typically developing fetuses, making *multiple 24-hr recordings per week for each participant* throughout the third trimester of brain development. The data collected in infancy for this proposal will serve as the foundation for an **R01 proposal** aimed to collect longitudinal data on auditory and language development at ages 2 and 5 years in these same infants, and to relate perinatal auditory exposures to communication outcomes in childhood.

**Innovation**

Comprehensive perinatal auditory experience. Although our proposed method to measure preterm infants' auditory exposures in the NICU using LENA devices has been employed by others,[43 44] accurate estimates of comprehensive individual auditory experience are lacking due to the limited number of 16-hr recordings measured for each subject. In the present study we will amass an unprecedented amount of auditory exposure data for each subject by measuring multiple 24-hr periods per week throughout NICU stay.

Fetal language exposures. LENA devices have been used to track language exposure for infants and children, but no data yet exist on language exposure for typically developing fetuses. This study will provide these data.

Effects of perinatal auditory experience. Theory holds that abnormal perinatal auditory input influences early brain development, as indicated by animal models. The data collected here will provide a rare opportunity to assess the effects of altered perinatal auditory input on brain development in humans.

Normative ABR data at 6 and 8 kHz. There is growing interest in incorporating 6- and 8-kHz tone bursts with diagnostic ABRs for infants, but normative data are not yet widely available. We will collect these data.

**Approach**

**Aim 1: Determine the difference between intrauterine and NICU auditory exposures for human infants**

**General Methods:** Power analysis. Our preliminary study on NICU auditory exposures (see Experiment 1A below) had an effect size >1.0. A previous study on NICU auditory exposures showed a smaller effect size of 0.48.[43] A sample size of 69 subjects per group yields power of 0.80 to detect the smaller effect size of 0.48.

Participants. The preterm group will consist of 100 very preterm (VPT) infants (born <32 weeks' gestation). We focus on VPT infants because risks for impaired neurodevelopment increase substantially for VPT infants. Participant families will be recruited from the Carle Foundation Hospital NICU in Urbana, Illinois. Infants will be

excluded if they have a known or suspected congenital anomaly, infection, or prenatal brain lesion. On average, the Carle NICU admits >120 VPT infants annually. During our pilot phase, we recruited more than one VPT infant per week. We estimate recruitment of 50 VPT infants annually. The control group will consist of 100 healthy pregnant women <32 weeks pregnant and their FT babies. Participants will be recruited from the Urbana-Champaign community and will be compensated for participation. Data collected from subjects who ultimately undergo premature labor (<37 weeks) will be excluded.

NICU auditory exposures and medical factors. The following procedures are approved by the Carle NICU research and nursing staff and do not interfere with medical care practices (see Letter of Support from Co-I Dr. Rollo). A LENA device, which is a small 2-oz recording device capable of capturing 24 hours of high-fidelity, calibrated continuous audio data, will be adhered to the inside wall of the infant's incubator or crib, near the head of the infant. Each 24-hr LENA recording will be processed with an automated classification algorithm that calculates the durations of different sound categories: language, electronic sounds, noise, and silence.[73 74] Recordings will be made three times per week throughout NICU stay. While infants in our NICU are generally treated within the incubator or crib, they are removed for skin-to-skin sessions with a parent. When the infant is removed for skin-to-skin, the nurse will remove the device and adhere it to the armchair, near the infant's head.

Infant medical factors will be collected to include as covariates for statistical analyses, including: characterization of labor, delivery, and resuscitation; data on respiratory, cardiovascular, nutritional, and infectious disease care, including respiratory device use; growth of the infant; length of NICU stay; use of blindfolds; transitions to environments with greater lighting; and cranial ultrasound findings. Particular attention will be given to bilirubin levels and ototoxic drug (*e.g.*, gentamicin, furosemide) administration as these factors have known associations with hearing loss.[75 76] Maternal characteristics will be documented, including maternal age, marital status, socioeconomic status, level of education, prenatal drug exposure, family structure and maternal medical history. All preterm infants undergo routine ABR hearing screening prior to discharge from the NICU. Hearing screening results will be documented.

Parent presence and skin-to-skin care will be documented in two ways. First, a daily parent care log stored at the bedside will be used to record the frequency and duration of parental presence and holding. Parents will be asked to complete this log, with assistance from the nurse as needed. This information will be supplemented by each infant's electronic medical record, in which nurses document parents' visits and activities.

Fetal auditory exposures. A LENA device attached to a necklace will be worn around the neck so as to be near the abdomen of the pregnant female subject for a 24-hr period. Any necessary removal of the device lasting more than five minutes (*e.g.*, to shower) will be documented by the subject. During sleep, the LENA will be placed at the bedside. Recordings will take place twice per week throughout the third trimester of pregnancy. Compliance will be assessed with periodic reminder alerts to and from the participant *via* instant messaging. Extrauterine recordings may not reflect actual intrauterine exposures. Because the LENA can be calibrated to provide absolute intensity levels, we will apply a womb-like filter to our recordings[1] and remove any data where all spectral levels are below the putative noise floor of the womb.

Parental and family factors. Parents in both study groups will be surveyed about a range of pregnancy- and family-related issues, including pregnancy history; maternal age; family social, educational, and economic circumstances; parental perceptions of stress in the NICU or during pregnancy; and maternal anxiety/depression.

**Experiment 1A**

*Hypothesis:* Language exposure in the NICU is less than that experienced *in utero*.

*Premise and rationale:* Our approach follows from our preliminary data (**Fig. 1**). Fetal data were collected from 12 pregnant women who wore the LENA device twice per week for up to 14 weeks during the third trimester, accruing ~7000 hrs of data. VPT data were collected from 9 VPT infants with LENAs placed in their incubators/cribs thrice per week for up to 8 weeks, accruing ~2600 hrs of data. Average daily language exposures for VPT and fetal groups were 3.1 and 4.5 hrs, respectively.

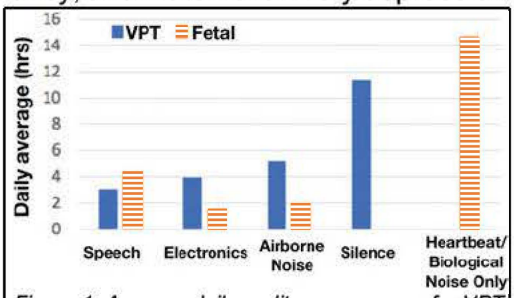



*Figure 1 Average daily auditory exposures for VPT infants and for typically developing fetuses*

These observations are significant for two reasons. First, although it is presumed that language exposure in the NICU is low,[43 44] language exposure for typically developing fetuses has been unknown. These data indicate ~45% greater language exposure for fetuses than for VPT infants. Second, these data highlight the changes to auditory input for VPT infants. For example, airborne noise exposure increases by a factor of 2.5 for VPT infants (see **Fig. 1**). VPT infants spend 11.5 hrs per day in silence, a condition that never occurs *in utero*. Fetal exposures during extrauterine silence consist of low-frequency biological sounds of heartbeat, digestion, *etc.*[17]

*Experimental Design:* We will determine daily auditory exposures for VPT infants and fetuses using the data

collection procedure outlined above. We will test for group differences in mean daily language exposure using a linear mixed-effects model. We will control for socioeconomic status and maternal education level in our model. We will also test for group differences in the proportion of male *vs.* female speech exposure. Talker sex effects have been reported for infants in the home,[77] but it is unknown whether effects hold for fetuses or VPT infants.

*Expected Outcome:* This experiment will establish the nature of auditory exposures for typically developing fetuses, offering a comparison for auditory exposures for our VPT group. Based on our preliminary data, we expect to find greater exposure to language for fetuses. These data will also allow us to characterize other potential differences between our groups (*e.g.*, electronic sounds) and/or trends within group (*e.g.*, change in daily language exposure for fetuses over time).

*Limitations and Alternative Plans:* We have found success with our approach for preliminary data collection. One challenge is that a LENA in an incubator may not capture sounds of nasal cannulas which generate sound at the infant's ear. We will document use of respiratory devices and will relabel periods of "Silence" during respiratory device use as "Noise." We can also assess SPL exposure with these data.

**Experiment 1B**

*Hypothesis:* Language, noise, and other sound exposures follow a circadian pattern for fetuses, but not for VPT infants.

*Premise and rationale:* The evidence for this hypothesis comes from our preliminary observations (**Fig. 2**). We conducted a time-varying analysis of hourly language, airborne noise, and total extrauterine sound exposure for 3 fetuses and 3 preterm infants, averaging across at least twenty 24-hr cycles for each subject. Whereas language, airborne noise, and total extrauterine sound exposure cycles for fetuses (solid lines) showed a marked circadian pattern, with low exposure during nighttime hours, VPT infants (dashed lines) showed little change across the cycle. To quantify this pattern, we calculated a "circadian index" for each subject and each category as the proportion of total daily exposure occurring during the most "active" 16-hr window. Mean circadian indices across 3 fetuses were 0.99, 0.94, and 0.97 for language, noise, and total sound exposure, respectively. Mean indices across 3 VPT infants were 0.75, 0.70, and 0.68 for these respective categories.

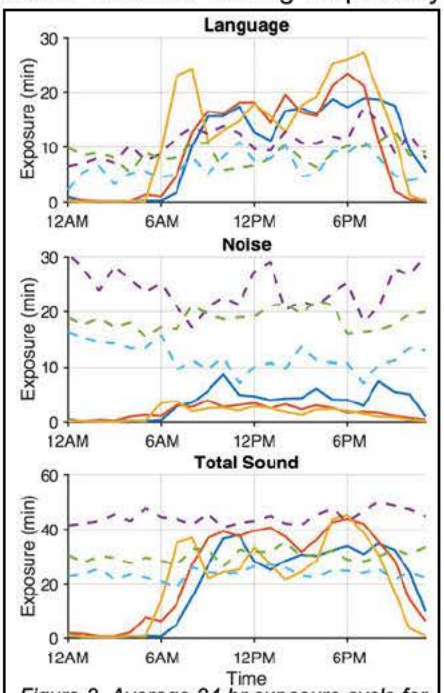



*Figure 2 Average 24 hr exposure cycle for language (top) noise (middle) and all extra uterine sounds (bottom) for 3 fetuses (solid lines) and 3 VPT infants (dashed lines)*

Although light/dark (visual) cycles have been studied in the NICU and have been shown to affect health outcomes,[78-80] these preliminary results demonstrate a lack of acoustic circadian rhythms for NICU infants. Such dramatic differences between VPT infants and fetuses are striking because, absent maternal hormonal signals important for the typical fetal brain to develop a circadian rhythm during the third trimester of gestation,[81] acoustic stimuli, along with visual stimuli, could potentially serve as a useful compensatory sensory cue for entrainment to a circadian rhythm.[80] It is important to note that nighttime hours for the fetus are not silent, but sounds are limited primarily to low-frequency cardiovascular and other biological sounds. It is not clear what direct influence, if any, extrauterine acoustic circadian rhythmic activity has on the fetus.

*Experimental Design:* We will test for group differences in circadian indices for language exposure, airborne noise exposure, and total extrauterine sound exposure using multiple linear regression models.

*Expected Outcome:* We expect to find an increase in circadian proportions for our fetal group. Because we are documenting parental presence and skin-to-skin care, our data will also allow us to characterize circadian trends in these variables (*e.g.*, if mother visits at the same time each day). It may be that increased parental presence is associated with increased language exposure.

*Limitations and Alternative Plans:* Since VPT infants in our NICU spend the majority of their time in the incubator or crib (including for diaper changing, cares, *etc.*), the LENA should provide an accurate account of auditory exposures. VPT infants are removed for skin-to-skin care, and the LENA will be moved and adhered to the parent's chair when this occurs. Infants may be moved for other procedures that preclude data collection during that period of time (*e.g.*, MRI). These procedures and time away from LENA will be documented. Any period away from the LENA lasting longer than five minutes will be excluded from analysis. The LENA sound classification algorithm has been tested and validated, showing good correspondence with ratings from trained listeners,[73 74] but we can conduct our own validation. Because VPT infants spend a large percentage of time sleeping,[82] many exposures occur during sleep. We recognize that it is not yet clear what differential effects auditory exposures may have during sleep *vs.* wakefulness for VPT infants (or fetuses).

**Experiment 1C**

*Hypothesis:* Exposure to sounds ≥400 Hz in the NICU increases with time between birth and discharge as VPT infants transition from enclosed infant incubators (less stable condition) to open cribs (more stable condition).

*Premise and rationale:* We assessed the transmission of sound into NICU incubators (*i.e.*, the transfer function) by conducting spectral analysis of simultaneous internal and external recordings of white noise and conversational speech presented over a loudspeaker located external to the incubator (**Fig. 3)**. As expected, the analysis revealed nonuniform attenuation as a function of frequency. Greatest attenuation of ~25 dB was at 400 Hz, with attenuations ranging 10-25 dB for frequencies beyond ~500 Hz. The measured transfer function was fairly consistent across loudspeaker locations around the incubator. For comparison with extra-to-intrauterine transfer functions, previously published mean data measured in humans (green) and sheep (dashed lines) are plotted in **Fig. 3**.

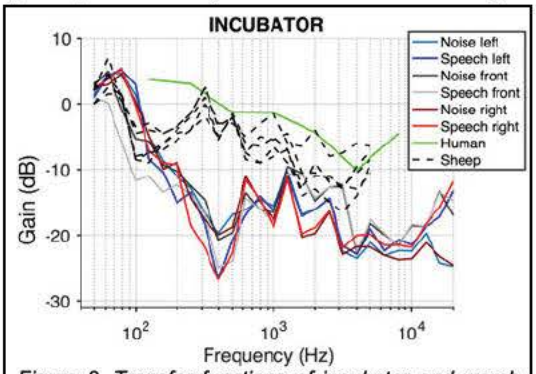



*Figure 3 Transfer functions of incubator and womb Separate incubator measurements were made with noise or speech source located on the left front or right side Uterine functions taken from data measured in humans[1] (green) and sheep[2] (dashed lines)*

These findings are of interest because it has been proposed that the NICU imposes an overexposure to very high frequencies,[83] whereas in the womb these frequencies may be at least somewhat attenuated. These data reveal that this assertion may only hold for later PMAs when preterm infants have graduated from the incubator to an open crib. This analysis also suggests a potential acoustical benefit of NICU incubators. It may be that this sound attenuation is a protective influence over a developing auditory system from noxious NICU sound levels that have long been a concern.[84] [85] Importantly, however, our data were collected in unoccupied incubators, absent of other life-supporting devices that generate broadband noises (*e.g.*, respiratory devices). Thus our preliminary observations require confirmation within occupied incubators. This experiment is designed to assess exposure to different frequency bands as a function of PMA.

*Experimental Design:* Third-octave band analysis will be conducted on each LENA recording for each subject using a previously established method with the long-term averaged spectrum.[86] This method yields average SPLs for individual third-octave bands for each recording, permitting the tracking of low- and high-frequency levels throughout NICU stay. We will test for a relationship between third-octave band levels and PMA using linear mixed-effect models that account for correlations by allowing for nesting of repeated observations within third-octave band and third-octave bands within subject.

*Expected Outcome:* We anticipate that sound levels for third-octave bands ≥400 Hz will increase with increasing PMA, while those bands <400 Hz will show little to no change over time.

*Limitations and Alternative Plans:* Due to LENA hardware limitations, only spectral data out to 8 kHz can be recorded. Although spectral energy beyond 8 kHz is often low, we will ascertain typical levels for the 8- and 16-kHz octave bands for our NICU using cross-sectional measurements with a sound level meter.

**Aim 2: Determine the effect of VPT birth on auditory neurodevelopment**

*Hypothesis:* VPT birth leads to longer latency tone burst ABRs at 52 weeks PMA.

*Premise and rationale:* It is established that click-evoked ABR latencies are longer for preterm infants than for FT born infants.[61] [63] [64] This suggests disrupted maturation of the cochlea, the hair cell-auditory nerve synapse, and/or the auditory brainstem for preterm infants.[87] Nearly all studies examining the effect of preterm birth on ABRs have used only click stimuli, leading to a paucity of frequency-specific information. This information is important to obtain because hair cells in the basal end of the cochlea are the most vulnerable to damage in many forms of hearing loss. Furthermore, there is reason to believe high frequencies are particularly affected in VPT infants. Ototoxicity and hearing loss resulting from aminoglycoside administration in children has been shown to largely affect high frequencies.[88] In some cases, loss can only be detected using extended high-frequency audiometry.[89] Because gentamicin (an aminoglycoside) is administered to preterm infants with infections, examination of the high frequencies in VPT infants is warranted.

*Experimental Design:* All audiological assessments will be conducted by our pediatric audiologist. VPT and FT infants will return for follow-up, targeting an age of 52 weeks PMA. Standard otoscopy, tympanometry, and otoacoustic emissions assessments will be conducted. ABRs will be collected during natural sleep using clicks at 80 and 25 dB nHL, and tone bursts at 80, 50, and 25 dB nHL at 0.5, 1, 2, 4, 6, and 8 kHz for each ear. Our protocol is based on established methods,[90] [91] developed under advisement of our consultant, Dr. Brown. Thresholds will be obtained for infants who do not show replicable responses at 25 dB nHL. We will prioritize data collection for 6 and 8 kHz first, followed by lower and midrange frequencies. With our protocol, we have successfully collected data at all frequencies for 11 out of 12 FT babies. We will test for group differences in tone burst wave V latencies using linear mixed-effects models that account for correlations by allowing for nesting of

repeated observations within each ear and ears within subject. We will test for an interaction between group and frequency. Because our main interest is whether VPT birth affects auditory neurodevelopment in the absence of other pathologies, we will exclude from these analyses any infant (VPT or FT) meeting criteria for a clinical diagnosis of hearing loss (nHL > 25 dB). Due to potential sex effects,[92] we will control for infant sex in our models.
*Expected Outcome:* We expect we will observe longer tone burst ABR latencies for VPT infants, with larger effects at frequencies ≥4 kHz. We suspect there will be hearing loss in our VPT group at 6 and 8 kHz due to ototoxic drug administration. During future follow up with this cohort (for our R01 proposal), we will also be able to assess the association between ABRs in infancy and childhood communication development.[93]
*Limitations and Alternative Plans:* Obtaining non-sedated ABRs for infants requires feeding and lulling to sleep. It is likely we will be unable to obtain all measurements for some infants due to fussiness or other factors. As done with our preliminary data collection, we will leave the mid-range frequencies as our final measurements and schedule an additional follow-up if we experience challenges obtaining data. We may also need to decrease the number of levels tested. We may detect hearing loss. To rule out middle-ear pathologies, we will use otoscopy and tympanometry, rescheduling the ABR if the infant fails tympanometry. Infants with hearing loss will be excluded from our regression analysis. For ABR peak-picking reliability, we will use two blinded judges.

**Aim 3: Determine the relationship between perinatal auditory exposures and auditory neurodevelopment**
*Hypothesis:* Greater language exposure during perinatal development leads to more rapid auditory neurodevelopment.
*Premise and rationale:* Justification for this experiment and hypothesis stems directly from our preliminary observations with ABR data collected from 11 of our 12 FT infants whose mothers participated in the LENA data collection described in Aim 1. Infants were brought back for ABR follow up at 52 weeks PMA. The data reveal a clear trend for a relationship between greater average daily language exposure during the third trimester of gestation and shorter left-right averaged absolute latencies for waves I, III, and V obtained with clicks at 80 dBnHL (**Fig. 4**). This trend held for both left and right ears individually as well (data not shown). These preliminary findings are striking because they raise the possibility that language exposure prior to birth facilitates maturation of the auditory pathway for humans, with long-lasting effects. Although the theoretical mechanism for this relationship is not clear, animal models have demonstrated that auditory brainstem and/or cortical neurophysiology[94] and absolute response latencies [31 95] can be modified by pre- and perinatal enriched or impoverished acoustic environments.

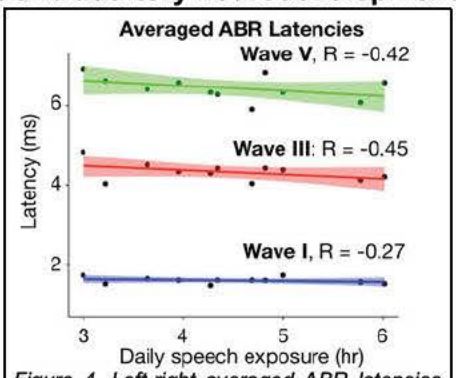


*Figure 4 Left right averaged ABR latencies for waves I (blue) III (red) and V (green) plotted against daily speech exposure Shading represents 95% confidence intervals*

*Experimental Design:* Although we observe an apparent relationship in our preliminary data with our FT infants, it is likely that 12 weeks of postnatal experience had an effect on auditory brainstem development. To mitigate this confound, in addition to ABR data collection at 52 weeks, we will conduct click-evoked ABRs at 44 weeks PMA when FT postnatal and VPT post discharge experience has less of an effect. We will test for an association between mean daily language exposure during the perinatal period and click-evoked ABR absolute and interpeak latencies at 44 weeks PMA and 52 weeks PMA using separate multiple linear regression models. We will conduct separate analyses for VPT infants and FT infants. For the FT group, we will control for birth gestational age and PMA at test date. For our VPT group, we will control for birth gestational age, PMA at test date, and other medical factors in our models, including length of NICU stay, ototoxic drug administration, type of nutrition (breast milk *vs*. donor milk *vs*. formula), and weight gain.
*Expected Outcome:* We predict a relationship between perinatal language exposure and click ABR latencies.
*Limitations and Alternative Plans:* We were surprised by this preliminary result and we recognize the theoretical mechanism for the observed relationship is not clear. The relationship was not observed for interpeak latencies. Nonetheless, we maintain this exploratory hypothesis as it derives directly from our pilot data. As an alternative, we can use SPL exposure, noise, and/or silence (for the VPT group) to predict ABR latencies. Additionally, in our longitudinal follow-up R01 proposal we plan to assess language/vocal development in later infancy and childhood using measures developed by our consultant, Dr. Ambrose.[96] Perinatal exposure data collected here will allow us to test for relationships between perinatal language exposure and childhood language development. It may be challenging to bring newborns in for two ABR visits, particularly for VPT infants. At 44 weeks we will restrict our data collection to only click-evoked ABRs to minimize time. Alternatively, we can assess postnatal language exposure prior to 52 weeks by using LENAs in the infants' homes following FT birth or NICU discharge.

**General Alternative Plans:** Many additional analyses could be conducted with the data collected here (*e.g.*, SPL exposure and relation to outcome). Critically, the Aims will yield these valuable, much-needed, yet presently unavailable data for these analyses, regardless of the outcome of our present scientific predictions.

# PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

| | |
|---|---|
| Are Human Subjects Involved | ● Yes ○ No |
| Is the Project Exempt from Federal regulations? | ○ Yes ● No |
| Exemption Number | ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 |
| Other Requested Information | |

**Human Subject Studies**

| Study# | Study Title | Clinical Trial? |
|---|---|---|
| 1 | Auditory experience during the prenatal and perinatal period | No |

## Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Auditory experience during the prenatal and perinatal period

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

| | | |
|---|---|---|
| 1.4.a. Does the study involve human participants? | ● Yes | ❍ No |
| 1.4.b. Are the participants prospectively assigned to an intervention? | ❍ Yes | ● No |
| 1.4.c. Is the study designed to evaluate the effect of the intervention on the participants? | ❍ Yes | ● No |
| 1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome? | ❍ Yes | ● No |

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

## Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- Premature birth

2.2. Eligibility Criteria

Preterm infants:
- birth less than 32 weeks gestational age
- no known or suspected congenital anomaly
- no congenital infection (e.g., syphilis, HIV, TORCH)
- no known prenatal brain lesion (e.g., cysts or infarctions)

Pregnant women:
- greater than 18 years of age
- permanent residents of Champaign or Illinois
- less than 32 weeks pregnant
- no history of mental disease, drug abuse, or other chronic health conditions
- no current complications in pregnancy

| | | |
|---|---|---|
| 2.3. Age Limits | Min Age: N/A (No limit) | Max Age: N/A (No limit) |
| 2.4. Inclusion of Women, Minorities, and Children | Inclusion_of_women_minorities_children.pdf | |
| 2.5. Recruitment and Retention Plan | Recruitment_and_retention_plan.pdf | |
| 2.6. Recruitment Status | Recruiting | |
| 2.7. Study Timeline | Study_timeline.pdf | |
| 2.8. Enrollment of First Subject | 10/03/2018 | Actual |

## INCLUSION OF WOMEN AND MINORITIES

**Very preterm infants**
Based on the demographics of the Champaign-Urbana area (American Indian-0.3%; Asian-8.9%; Black-12.4%; Native Hawaiian-0.1%; White-73.4%; Hispanic Ethnicity–5.3%; Not Hispanic or Latino-94.7%), which is the anticipated distribution of preterm infants, the planned enrollment is as shown in the Planned Enrollment table. We will make every effort to seek out participants from ethnic and racial groups who are admitted to the Carle neonatal intensive care unit (NICU). After identifying suitable families of eligible preterm infants admitted to the NICU, Carle research staff will approach and invite the family to participate in the proposed experiment. The initial approach will detail the nature and duration of the experiment, any potential benefits and risks, as well as their rights as study participants. Given the admission rates at the Carle NICU (>120 very preterm infants annually), we believe we will be able to recruit a subject pool based on the planned enrollment. We expect no difficulty in recruiting male and female subjects in equal numbers.

**Pregnant women and full-term infants**
Based on the demographics of the Champaign-Urbana area (American Indian-0.3%; Asian-8.9%; Black-12.4%; Native Hawaiian-0.1%; White-73.4%; Hispanic Ethnicity–5.3%; Not Hispanic or Latino-94.7%), which is the anticipated distribution of pregnant women, the planned enrollment is as shown in the Planned Enrollment table. We will make every effort to seek out participants from ethnic and racial groups. We will post flyers in maternity clinics, schools, and libraries located throughout the Champaign-Urbana area, including public schools and clinics/libraries located in low-income neighborhoods. After identifying suitable subjects, the initial visit will detail the nature and duration of the experiment, any potential benefits and risks, as well as their rights as study participants.

## INCLUSION OF CHILDREN

**Very preterm infants**
Children will be included in this group. We include infants born less than 32 weeks' gestation because risks for cognitive deficits and other adverse health outcomes drop substantially for infants born after this gestational age. On our investigative team we have a neonatologist and a neuroscientist with training and clinical research experience with preterm infants. We also have a pediatric audiologist collecting audiological data. Thus we bring substantial expertise for working with children of this age.

**Pregnant women and full-term infants**
Children will be included in this group as we will collect audiological data on the full-term born infants of our pregnant female subjects. These full-term infants will serve as a control group for our preterm infant population. Pregnant children (*i.e.*, pregnant females age 18 and under) will *not* be included in pregnant women group. We exclude pregnant children in this case because of the added emotional strain and unique social consequences of teen pregnancy, which would likely affect the pregnant child's social behavior and willingness and/or ability to complete the study.

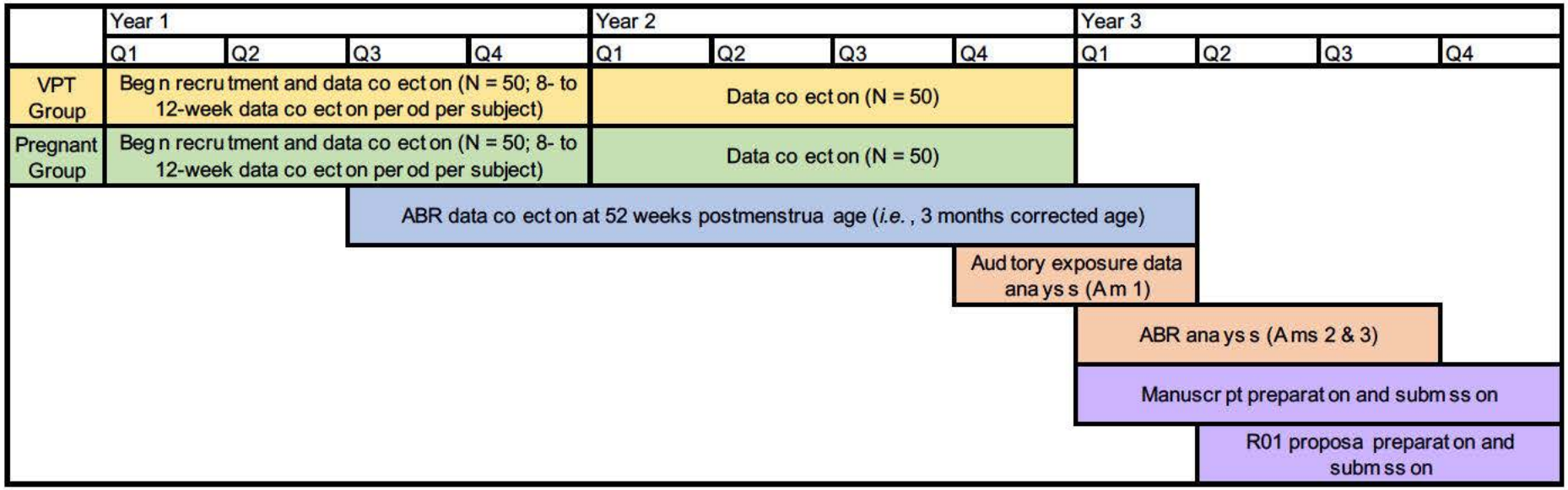
## RECRUITMENT AND RETENTION PLAN

### Very preterm infants

Families of infants who meet the eligibility criteria will initially be identified by the attending neonatologist or nurse at Carle Hospital, who will discuss the study with the family and then refer the family to the clinical research coordinator or research nurse practitioner at Carle Hospital. The coordinator or nurse practitioner, along with University of Illinois research staff, will provide further information about the study and obtain informed consent from families interested in participating. For retention, research staff will periodically follow-up with families to assess their satisfaction with study participation. A small care package consisting of child toys, a book, thank-you card, *etc.*, will be provided to each family after discharge who completes the NICU portion of the study. Families will be reminded after discharge of the 3-month follow up visit to the audiology clinic.

### Pregnant women and full-term infants

Participants will be recruited through word-of-mouth and via public postings, media, and the Internet. Flyers will be posted in maternity clinics, schools, and libraries located throughout the Champaign-Urbana area. Potential participants will initiate contact with research team members if interested in participating in the study. During the initial contact, the research team member will provide further information about the study, assess eligibility, and schedule a meeting to obtain informed consent for eligible women interested in participating. For retention, research staff will periodically follow-up with subjects to assess their satisfaction with study participation. Subject remuneration may increase slightly after four weeks of participation to facilitate retention. A small care package consisting of child toys, a book, thank-you card, *etc.*, will be provided to each mother after delivery who completes the pregnancy portion of the study. Along with the care package, mothers will be provided a reminder of the 3-month follow up visit to the audiology clinic.


Year 1
Year 2
Year 3
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
VPT Group
Begin recruitment and data collection (N = 50; 8- to 12-week data collection period per subject)
Data collection (N = 50)
Pregnant Group
Begin recruitment and data collection (N = 50; 8- to 12-week data collection period per subject)
Data collection (N = 50)
ABR data collection at 52 weeks postmenstrual age (i.e., 3 months corrected age)
Auditory exposure data analysis (Aim 1)
ABR analysis (Aims 2 & 3)
Manuscript preparation and submission
R01 proposal preparation and submission

**Inclusion Enrollment Reports**

| IER ID# | Enrollment Location Type | Enrollment Location |
|---|---|---|
| Study 1, IER 1 | Domestic | Champaign-Urbana, Illinois |
| Study 1, IER 2 | Domestic | Champaign-Urbana, Illinois |
| Study 1, IER 3 | Domestic | Champaign-Urbana, Illinois |

## Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ❍ Yes ● No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): Champaign-Urbana, Illinois

Comments: Very preterm infant group

**Planned**

| Racial Categories | Ethnic Categories | | | | Total |
|---|---|---|---|---|---|
| | Not Hispanic or Latino | | Hispanic or Latino | | |
| | Female | Male | Female | Male | |
| American Indian/ Alaska Native | 1 | 1 | 0 | 0 | 2 |
| Asian | 5 | 5 | 0 | 0 | 10 |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | 0 | 0 | 2 |
| Black or African American | 6 | 6 | 0 | 0 | 12 |
| White | 34 | 34 | 3 | 3 | 74 |
| More than One Race | 0 | 0 | 0 | 0 | 0 |
| **Total** | 47 | 47 | 3 | 3 | 100 |

**Cumulative (Actual)**

| Racial Categories | Ethnic Categories | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | Not Hispanic or Latino | | | Hispanic or Latino | | | Unknown/Not Reported Ethnicity | | | |
| | Female | Male | Unknown/ Not Reported | Female | Male | Unknown/ Not Reported | Female | Male | Unknown/ Not Reported | |
| American Indian/ Alaska Native | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| White | 5 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 |
| More than One Race | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | 5 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 |

## Inclusion Enrollment Report 2

Using an Existing Dataset or Resource* : ❍ Yes ● No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): Champaign-Urbana, Illinois

Comments: Pregnant women

**Planned**

| Racial Categories | Ethnic Categories | | | | Total |
|---|---|---|---|---|---|
| | Not Hispanic or Latino | | Hispanic or Latino | | |
| | Female | Male | Female | Male | |
| American Indian/ Alaska Native | 2 | 0 | 0 | 0 | 2 |
| Asian | 10 | 0 | 0 | 0 | 10 |
| Native Hawaiian or Other Pacific Islander | 2 | 0 | 0 | 0 | 2 |
| Black or African American | 12 | 0 | 0 | 0 | 12 |
| White | 68 | 0 | 6 | 0 | 74 |
| More than One Race | 0 | 0 | 0 | 0 | 0 |
| **Total** | 94 | 0 | 6 | 0 | 100 |

**Cumulative (Actual)**

| Racial Categories | Ethnic Categories | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | Not Hispanic or Latino | | | Hispanic or Latino | | | Unknown/Not Reported Ethnicity | | | |
| | Female | Male | Unknown/ Not Reported | Female | Male | Unknown/ Not Reported | Female | Male | Unknown/ Not Reported | |
| American Indian/ Alaska Native | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Asian | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| White | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 |
| More than One Race | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Unknown or Not Reported | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 12 |

## Inclusion Enrollment Report 3

Using an Existing Dataset or Resource* : ❍ Yes ● No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): Champaign-Urbana, Illinois

Comments: Full-term infants (birthed by our pregnant women group)

**Planned**

| Racial Categories | Ethnic Categories | | | | Total |
|---|---|---|---|---|---|
| | Not Hispanic or Latino | | Hispanic or Latino | | |
| | Female | Male | Female | Male | |
| American Indian/ Alaska Native | 1 | 1 | 0 | 0 | 2 |
| Asian | 5 | 5 | 0 | 0 | 10 |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | 0 | 0 | 2 |
| Black or African American | 6 | 6 | 0 | 0 | 12 |
| White | 34 | 34 | 0 | 0 | 68 |
| More than One Race | 0 | 0 | 0 | 0 | 0 |
| **Total** | 47 | 47 | 0 | 0 | 94 |

**Cumulative (Actual)**

| Racial Categories | Ethnic Categories | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | Not Hispanic or Latino | | | Hispanic or Latino | | | Unknown/Not Reported Ethnicity | | | |
| | Female | Male | Unknown/ Not Reported | Female | Male | Unknown/ Not Reported | Female | Male | Unknown/ Not Reported | |
| American Indian/ Alaska Native | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Asian | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| White | 5 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 |
| More than One Race | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Unknown or Not Reported | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | 5 | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 12 |

## Section 3 - Protection and Monitoring Plans (Study 1)

| | |
|---|---|
| 3.1. Protection of Human Subjects | Protection_of_human_subjects.pdf |
| 3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site? | ❍ Yes ● No ❍ N/A |
| If yes, describe the single IRB plan | |
| 3.3. Data and Safety Monitoring Plan | |
| 3.4. Will a Data and Safety Monitoring Board be appointed for this study? | ❍ Yes ● No |
| 3.5. Overall structure of the study team | |

## PROTECTION OF HUMAN SUBJECTS

### 1. Risks to Human Subjects

### 1a. Human Subjects Involvement, Characteristics, and Design

The proposed study is a prospective observational cohort study examining (1) the effect of premature birth on perinatal auditory exposures and auditory neurodevelopment, and (2) the effect of neonatal intensive care unit (NICU) auditory exposures on infant auditory function. The study population will consist of infants born very preterm (VPT; <32 week's gestation) because risks for cognitive deficits and other adverse health outcomes decrease substantially for infants born after 32 weeks gestational age. The control group will consist of pregnant women and their fetuses that will ultimately be born full-term. Our power analysis indicates we need a sample size of 69 per group to detect anticipated effect sizes. The target enrollment is 100 VPT infants and 100 pregnant women/full-term infants because we expect some attrition (*e.g.*, pregnant women who ultimately undergo premature labor).

The VPT infant group will be recruited from the Carle Foundation Hospital NICU under the supervision of Co-Investigator Derrick Rollo, MD, attending neonatologist, and Principle Investigator Brian Monson, PhD. NICU auditory exposure data collection will take place in the Carle NICU. The pregnant women will be recruited from the Champaign-Urbana community under the direction of Dr. Monson. Audiological assessments will take place at the University of Illinois at Urbana-Champaign (UIUC) Audiology Clinic at 52 weeks postmenstrual age (age 3 months for the full-term infant group, and 3 months corrected age for the VPT infant group), under the supervision of our Clinical Pediatric Audiologist Brittney Reidy, AuD, and Dr. Monson.

### 1b. Study Procedures, Materials, and Potential Risks

Auditory exposure data will be collected from all participants using small, wearable audio recording devices, called LENA devices. LENA devices will be placed inside the incubator or crib for NICU infants. The devices will be worn around the neck for pregnant women. Audio recordings will be made in this process. Additionally, medical histories, medical factors related to birth and delivery, and social factors will be collected from medical records and/or via questionnaires. Audiological data will be collected at 52 weeks postmenstrual age using standard pediatric audiological assessments.

For preterm infants, LENA devices will be sanitized prior to placement inside the incubator/crib using standard sanitizing procedures for NICU electronic equipment. Because audio recordings will be made, personal health information and private conversations may be recorded. To minimize risks of confidentiality, all audio data will be stored on HIPAA-compliant encrypted password-protected servers. Each participant will be given an ID number and all data will be recorded using only that ID number. Only those researchers involved in the project with proper human subjects and ethics training will have access to the data. Any hard copies of identifiable data will be stored in a locked cabinet in a locked office.

### 2. Adequacy of Protection Against Risk

### 2a. Informed Consent and Assent

VPT Infant Group

Parents of eligible VPT infant patients will be approached by their physician or nurse at the Carle Hospital NICU to inform them of the study. They will then be approached by the Carle Hospital clinical research coordinator or nurse practitioner to provide further information. Informed consent will be obtained by the clinical research coordinator or nurse practitioner for parents agreeing to participate in the study.

All participants will be fully informed of the purpose of and methods used in each experiment. The experimental protocol and informed consent procedure will be overseen by the local institutional review board (IRB) on the use of human subjects at the Carle Hospital. Participants will be encouraged to discuss any comments, criticisms or difficulties with the PI, Co-I, or research staff. Participants will be informed of PI's role and are encouraged to contact the PI in the event that they are dissatisfied by their treatment in any manner. All participants will be informed that they may withdraw from the study at any time, for any reason.

Pregnant Women/Full-term Infant Group

Potential pregnant women participants will initiate contact with the UIUC research team after learning of the study via advertisement or word of mouth. After assessing eligibility, an initial meeting will be scheduled with a

member of the UIUC research team to provide further information. Informed consent will be obtained by a member of the research team.

All subjects will be fully informed of the purpose of and methods used in each experiment. The experimental protocol and informed consent procedure will be overseen by the local IRB on the use of human subjects at UIUC. Subjects will be encouraged to discuss any comments, criticisms or difficulties with the PI or research staff. Subjects will be informed of PI's role and are encouraged to contact the PI in the event that they are dissatisfied by their treatment in any manner. All subjects will be informed that they may withdraw from the study at any time, for any reason.

**2b. Protection Against Risk**

The data collection procedures, including LENA devices and audiological assessments, represent minimal risk to the participants in this study. For preterm infants, LENA devices will be sanitized prior to placement inside the incubator/crib using standard sanitizing procedures for NICU electronic equipment. Based on our pilot data and previous studies conducted by others, the LENA device poses little to no risk of interference with medical procedures in the NICU. However, because audio recordings will be made, personal health information and private conversations may be recorded. To protect against risks of confidentiality, analysis of audio recordings will consist of automated procedures that require no listening to the audio recordings. To further protect against risks of confidentiality, all audio data will be stored on HIPAA-compliant encrypted password-protected servers. Each participant will be given an ID number and all data will be recorded using only that ID number. Only those researchers involved in the project with proper human subjects and ethics training will have access to the data. Any hard copies of identifiable data will be stored in a locked cabinet in a locked office.

For audiological assessments, some infants may exhibit discomfort or general fussiness. Our trained pediatric audiologist (Dr. Reidy) will conduct and oversee audiological assessments and will be able to help soothe the infant and/or determine when to cease the procedure.

**2c. Vulnerable Subjects**

*Pregnant Women, Fetuses, and Neonates*

This study is comprised of subjects that are pregnant women, fetuses, and neonates.

The use of a LENA device poses no known risks specific to pregnant women or fetuses beyond those of the pregnant woman carrying a small device (*e.g.*, a cell phone).

The use of a LENA device poses no known risks specific to neonates in the NICU beyond that of routine NICU medical care. Although we have yet to encounter such an incident, adhering a LENA device to the inner wall of an incubator using Command Strips presents the possibility that the device might fall. To protect against any risk, research and nursing staff will be trained to adhere the device securely to the wall using an ample amount of Command Strip tape and place the device in a location where a potential fall is unlikely to touch the infant.

Pediatric audiological assessments pose minimal risk to infants and are routinely conducted. We will have our trained pediatric audiologist conduct and oversee all audiological assessments.

**3. Potential Benefits of the Proposed Research to Research Participants and Others**

All parents whose infants undergo audiological assessments will receive a clinical diagnosis of their baby's hearing. Following participation in the study, all parents who desire to know their baby's auditory exposures prior to full term will be provided with this information. This information could help parents determine whether they wish to modify their baby's exposures (*e.g.*, by increasing language input).

**4. Importance of the Knowledge to be Gained**

The proposed research will greatly enhance our understanding of how prenatal and perinatal auditory experience affects auditory brain development and communication behavior. It will also provide critical information regarding how NICU auditory exposures differ from intrauterine auditory exposures, paving the way for interventions designed to optimize NICU auditory experience for preterm infants.

## Section 4 - Protocol Synopsis (Study 1)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

| Type | Name | Description |
|---|---|---|

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ❍ No

4.2.e. Intervention Model

4.2.f. Masking ❍ Yes ❍ No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

| Type | Name | Time Frame | Brief Description |
|---|---|---|---|

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ❍ Yes ❍ No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

**Delayed Onset Studies**

| Delayed Onset Study# | Study Title | Anticipated Clinical Trial? | Justification |
|---|---|---|---|
| The form does not have any delayed onset studies | | | |

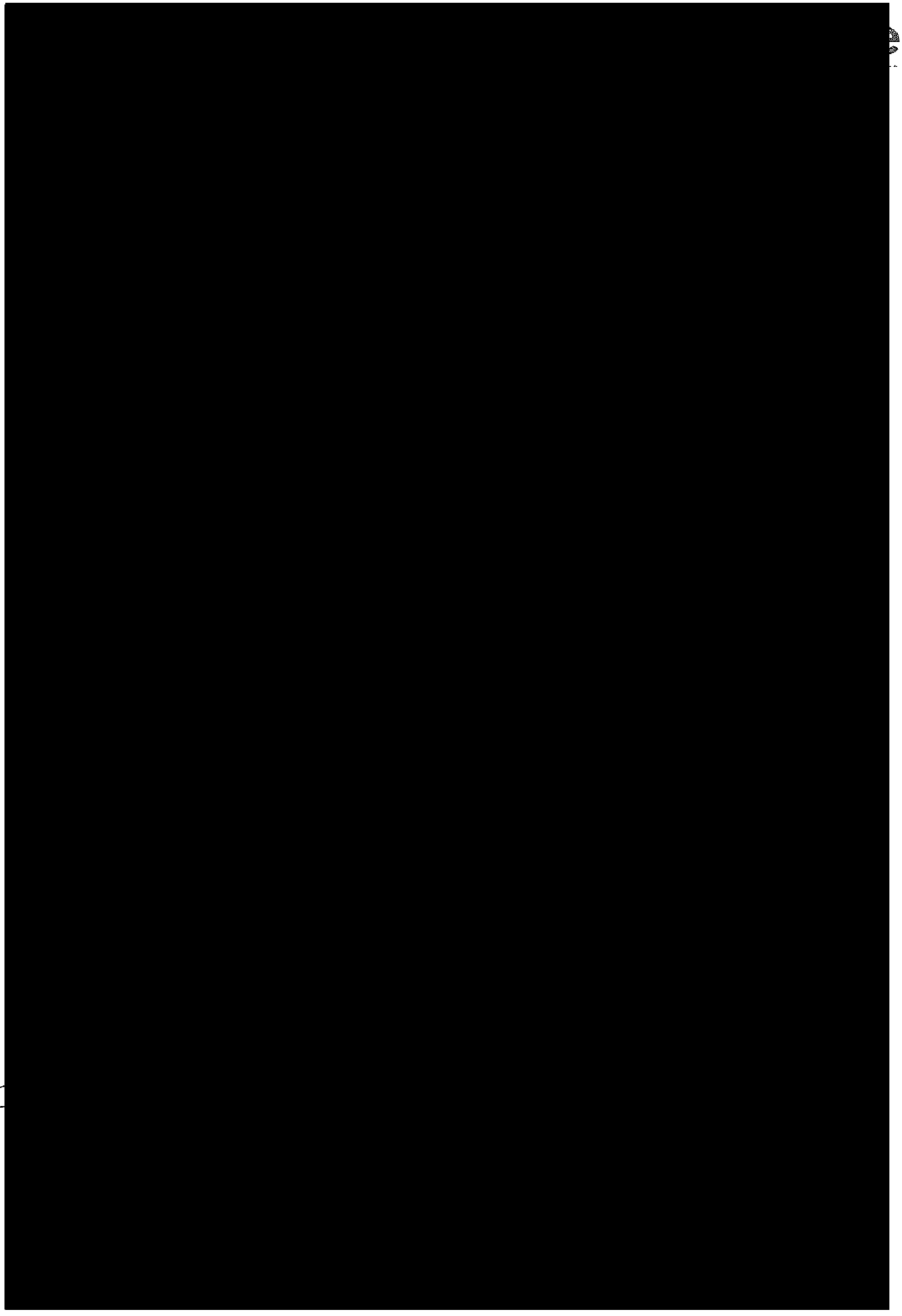
## BIBLIOGRAPHY


1. Richards DS, Frentzen B, Gerhardt KJ, McCann ME, & Abrams RM (1992) Sound levels in the human uterus. *Obstetrics and gynecology* 80(2):186-190.
2. Peters AJ, Gerhardt KJ, Abrams RM, & Longmate JA (1993) Three-dimensional intraabdominal sound pressures in sheep produced by airborne stimuli. *American journal of obstetrics and gynecology* 169(5):1304-1315.
3. Lecanuet JP*, et al.* (1998) What sounds reach fetuses: biological and nonbiological modeling of the transmission of pure tones. *Dev Psychobiol* 33(3):203-219.
4. Gerhardt KJ & Abrams RM (1996) Fetal hearing: characterization of the stimulus and response. *Seminars in perinatology* 20(1):11-20.
5. Leibold LJ & Werner LA (2012) Maturation of the auditory system. *Translational Perspectives in Auditory Neuroscience: Hearing Across the Life Span—Assessment and Disorders*, (Plural, San Diego), pp 29-62.
6. DeCasper AJ & Fifer WP (1980) Of human bonding: newborns prefer their mothers' voices. *Science* 208(4448):1174-1176.
7. Partanen E*, et al.* (2013) Learning-induced neural plasticity of speech processing before birth. *Proceedings of the National Academy of Sciences of the United States of America* 110(37):15145-15150.
8. Moon C, Lagercrantz H, & Kuhl PK (2013) Language experienced in utero affects vowel perception after birth: a two-country study. *Acta paediatrica* 102(2):156-160.
9. Lecanuet JP & Schaal B (1996) Fetal sensory competencies. *European journal of obstetrics, gynecology, and reproductive biology* 68(1-2):1-23.
10. Hepper PG & Shahidullah BS (1994) The development of fetal hearing. *Fetal and Maternal Medicine Review* 6(03):167-179.
11. Lecanuet JP, Granier-Deferre C, & Busnel MC (1988) Fetal cardiac and motor responses to octave-band noises as a function of central frequency, intensity and heart rate variability. *Early Hum Dev* 18(2-3):81-93.
12. Birnholz JC & Benacerraf BR (1983) The development of human fetal hearing. *Science* 222(4623):516-518.
13. Graziani LJ, Weitzman ED, & Velasco MS (1968) Neurologic maturation and auditory evoked responses in low birth weight infants. *Pediatrics* 41(2):483-494.
14. Starr A, Amlie R, Martin W, & Sanders S (1977) Development of auditory function in newborn infants revealed by auditory brainstem potentials. *Pediatrics* 60(6):831-839.
15. Gerhardt KJ & Abrams RM (2000) Fetal exposures to sound and vibroacoustic stimulation. *J Perinatol* 20(8 Pt 2):S21-30.
16. Gerhardt KJ, Abrams RM, & Oliver CC (1990) Sound environment of the fetal sheep. *American journal of obstetrics and gynecology* 162(1):282-287.
17. Querleu D, Renard X, Versyp F, Paris-Delrue L, & Crepin G (1988) Fetal hearing. *European journal of obstetrics, gynecology, and reproductive biology* 28(3):191-212.
18. Griffiths SK, Brown WS, Jr., Gerhardt KJ, Abrams RM, & Morris RJ (1994) The perception of speech sounds recorded within the uterus of a pregnant sheep. *The Journal of the Acoustical Society of America* 96(4):2055-2063.
19. Moon C, Cooper RP, & Fifer WP (1993) 2-day-olds prefer their native language. *Infant Behavior & Development* 16(4):495-500.
20. Decasper AJ & Spence MJ (1986) Prenatal maternal speech influences newborns perception of speech sounds. *Infant Behavior & Development* 9(2):133-150.
21. Mahmoudzadeh M*, et al.* (2013) Syllabic discrimination in premature human infants prior to complete formation of cortical layers. *Proceedings of the National Academy of Sciences* 110(12):4846-4851.
22. Hepper P (1988) Fetal" soap" addiction. *The Lancet* 331(8598):1347-1348.
23. Lalande NM, Hetu R, & Lambert J (1986) Is occupational noise exposure during pregnancy a risk factor of damage to the auditory system of the fetus? *Am J Ind Med* 10(4):427-435.
24. Daniel T & Laciak J (1982) [Clinical observations and experiments concerning the condition of the cochleovestibular apparatus of subjects exposed to noise in fetal life]. *Rev Laryngol Otol Rhinol (Bord)* 103(4):313-318.
25. Henderson D, Subramaniam M, & Boettcher FA (1993) Individual susceptibility to noise-induced hearing loss: an old topic revisited. *Ear Hear* 14(3):152-168.

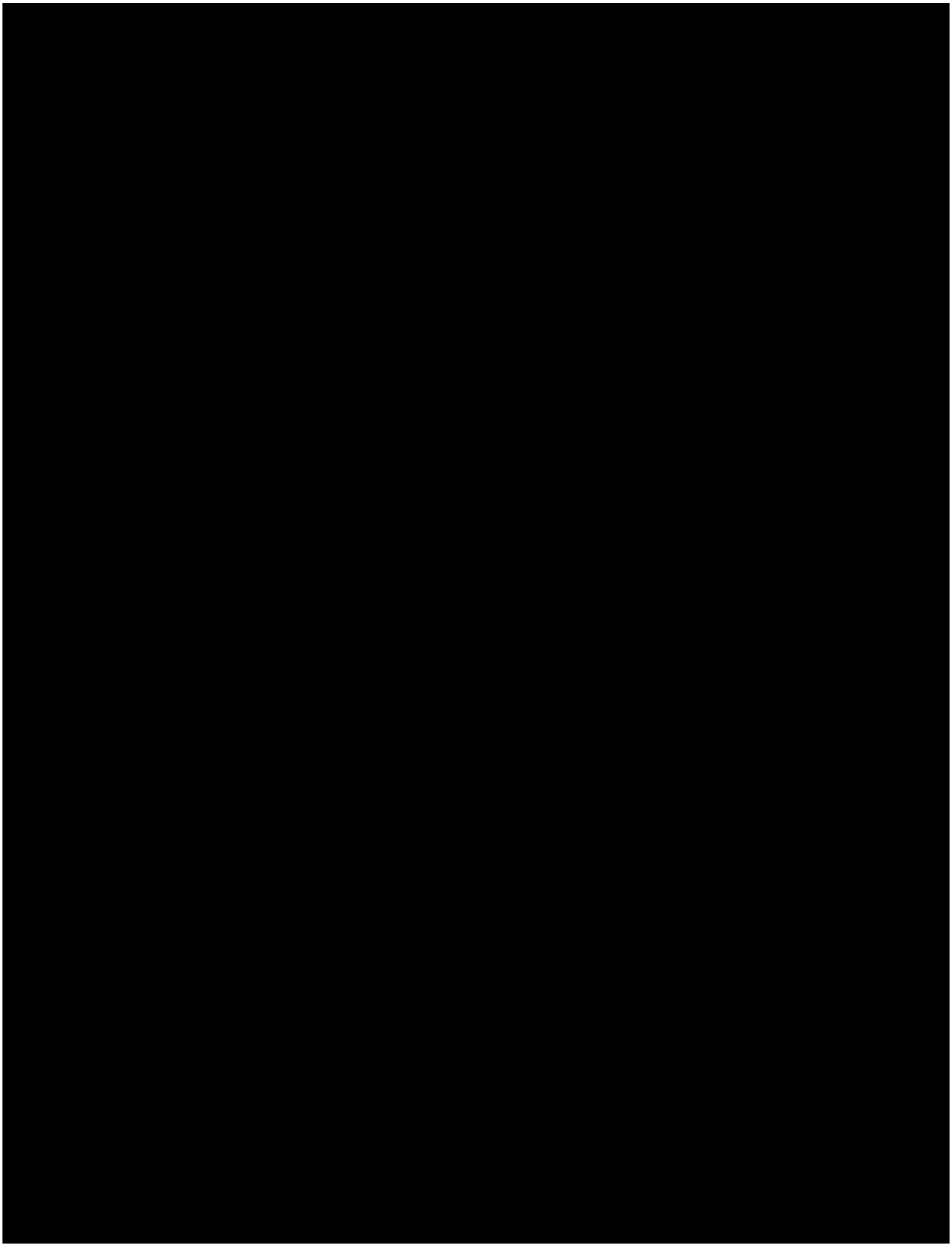
26. Cook RO*, et al.* (1982) Brainstem-evoked responses of guinea pigs exposed to high noise levels in utero. *Dev Psychobiol* 15(2):95-104.
27. Griffiths SK, Pierson LL, Gerhardt KJ, Abrams RM, & Peters AJ (1994) Noise induced hearing loss in fetal sheep. *Hear Res* 74(1-2):221-230.
28. Weitzman ED & Graziani LJ (1968) Maturation and topography of the auditory evoked response of the prematurely born infant. *Developmental Psychobiology* 1(2):79-89.
29. Jardri R*, et al.* (2008) Fetal cortical activation to sound at 33 weeks of gestation: a functional MRI study. *Neuroimage* 42(1):10-18.
30. Polley D, Seidl A, Wang Y, & Sanchez J (2013) Functional Circuit Development in the Auditory System. *Neural Circuit Development and Function in the Healthy and Diseased Brain: Comprehensive Developmental Neuroscience* 3:21.
31. Oliver DL, Izquierdo MA, & Malmierca MS (2011) Persistent effects of early augmented acoustic environment on the auditory brainstem. *Neuroscience* 184:75-87.
32. Ponton CW, Don M, Eggermont JJ, Waring MD, & Masuda A (1996) Maturation of human cortical auditory function: differences between normal-hearing children and children with cochlear implants. *Ear and hearing* 17(5):430-437.
33. Sharma A, Dorman MF, & Spahr AJ (2002) A sensitive period for the development of the central auditory system in children with cochlear implants: implications for age of implantation. *Ear and hearing* 23(6):532-539.
34. Born DE & Rubel EW (1985) Afferent influences on brain stem auditory nuclei of the chicken: neuron number and size following cochlea removal. *Journal of Comparative Neurology* 231(4):435-445.
35. McMullen NT & Glaser EM (1988) Auditory cortical responses to neonatal deafening: pyramidal neuron spine loss without changes in growth or orientation. *Experimental brain research* 72(1):195-200.
36. Mowery TM, Kotak VC, & Sanes DH (2015) Transient Hearing Loss Within a Critical Period Causes Persistent Changes to Cellular Properties in Adult Auditory Cortex. *Cerebral Cortex* 25(8):2083-2094.
37. Caras ML & Sanes DH (2015) Sustained Perceptual Deficits from Transient Sensory Deprivation. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 35(30):10831-10842.
38. Bose M*, et al.* (2010) Effect of the environment on the dendritic morphology of the rat auditory cortex. *Synapse* 64(2):97-110.
39. Chang EF & Merzenich MM (2003) Environmental noise retards auditory cortical development. *Science* 300(5618):498-502.
40. Mooney R (2009) Neurobiology of song learning. *Current opinion in neurobiology* 19(6):654-660.
41. Barkat TR, Polley DB, & Hensch TK (2011) A critical period for auditory thalamocortical connectivity. *Nature neuroscience* 14(9):1189-1194.
42. Lasky RE & Williams AL (2009) Noise and light exposures for extremely low birth weight newborns during their stay in the neonatal intensive care unit. *Pediatrics* 123(2):540-546.
43. Pineda R*, et al.* (2017) Auditory Exposure in the Neonatal Intensive Care Unit: Room Type and Other Predictors. *The Journal of pediatrics* 183:56-66 e53.
44. Caskey M, Stephens B, Tucker R, & Vohr B (2011) Importance of parent talk on the development of preterm infant vocalizations. *Pediatrics* 128(5):910-916.
45. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, & Oosterlaan J (2009) Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics* 124(2):717-728.
46. Cone-Wesson B*, et al.* (2000) Identification of neonatal hearing impairment: infants with hearing loss. *Ear and Hearing* 21(5):488-507.
47. van Dommelen P, Verkerk PH, van Straaten HL, & Dutch Neonatal Intensive Care Unit Neonatal Hearing Screening Working G (2015) Hearing loss by week of gestation and birth weight in very preterm neonates. *Journal of Pediatrics* 166(4):840-843 e841.
48. Veen S*, et al.* (1993) Hearing loss in very preterm and very low birthweight infants at the age of 5 years in a nationwide cohort. *International journal of pediatric otorhinolaryngology* 26(1):11-28.
49. van Noort-van der Spek IL*, et al.* (2017) Normal neonatal hearing screening did not preclude sensorineural hearing loss in two-year-old very preterm infants. *Acta paediatrica* 106(10):1569-1575.
50. Amatuzzi M, Liberman MC, & Northrop C (2011) Selective inner hair cell loss in prematurity: a temporal bone study of infants from a neonatal intensive care unit. *Journal of the Association for Research in Otolaryngology : JARO* 12(5):595-604.

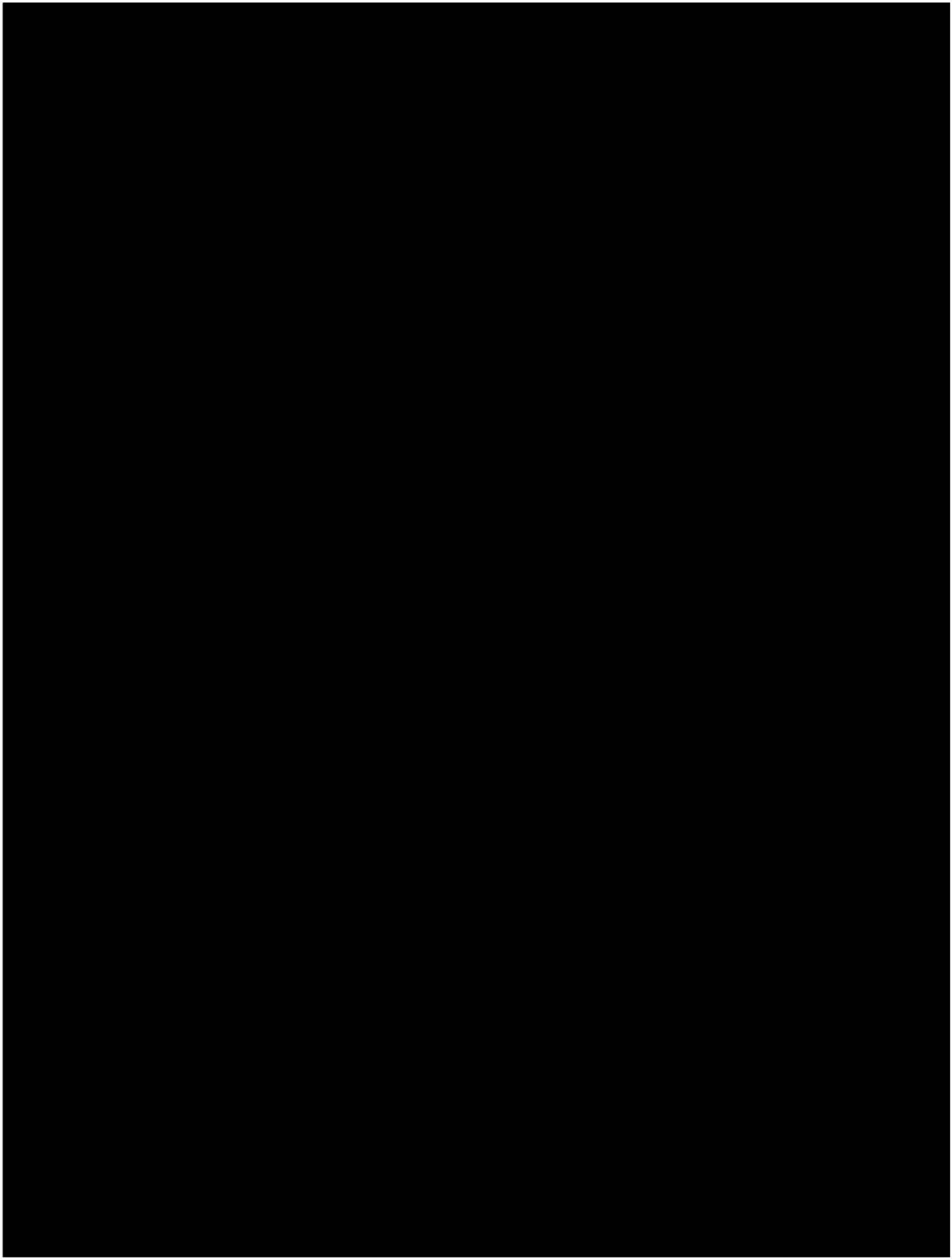
51. Xoinis K, Weirather Y, Mavoori H, Shaha SH, & Iwamoto LM (2007) Extremely low birth weight infants are at high risk for auditory neuropathy. *J Perinatol* 27(11):718-723.
52. Davis NM*, et al.* (2001) Auditory function at 14 years of age of very-low-birthweight children. *Developmental Medicine & Child Neurology* 43(3):191-196.
53. Bamiou D, Musiek F, & Luxon L (2001) Aetiology and clinical presentations of auditory processing disorders—a review. *Archives of disease in childhood* 85(5):361-365.
54. Dupin R, Laurent JP, Stauder JE, & Saliba E (2000) Auditory attention processing in 5-year-old children born preterm: evidence from event-related potentials. *Developmental medicine and child neurology* 42(7):476-480.
55. Barre N, Morgan A, Doyle LW, & Anderson PJ (2011) Language abilities in children who were very preterm and/or very low birth weight: a meta-analysis. *The Journal of pediatrics* 158(5):766-774 e761.
56. Vohr B (2013) Speech and language outcomes of very preterm infants. *Seminars in fetal & neonatal medicine*.
57. Vohr BR (2016) Language and hearing outcomes of preterm infants. *Seminars in perinatology* 40(8):510-519.
58. Tognola G*, et al.* (2005) Cochlear maturation and otoacoustic emissions in preterm infants: a time–frequency approach. *Hearing research* 199(1):71-80.
59. Abdala C, Oba SI, & Ramanathan R (2008) Changes in the DP-gram during the preterm and early postnatal period. *Ear Hear* 29(4):512-523.
60. Jiang ZD, Brosi DM, Wu YY, & Wilkinson AR (2009) Relative maturation of peripheral and central regions of the human brainstem from preterm to term and the influence of preterm birth. *Pediatric research* 65(6):657-662.
61. Stipdonk LW*, et al.* (2016) Auditory brainstem maturation in normal-hearing infants born preterm: a meta-analysis. *Developmental medicine and child neurology* 58(10):1009-1015.
62. Wang C & Jiang ZD (2018) Brainstem auditory abnormality in extremely premature babies and the impact of neonatal bronchopulmonary dysplasia. *Acta Obstet Gynecol Scand* 97(5):545-551.
63. Seethapathy J, Boominathan P, Uppunda AK, & Ninan B (2019) Changes in Auditory Brainstem Response in very preterm and late preterm infants. *International journal of pediatric otorhinolaryngology* 121:88-94.
64. Eggermont JJ & Salamy A (1988) Maturational time course for the ABR in preterm and full term infants. *Hearing Research* 33(1):35-47.
65. Pasman JW, Rotteveel JJ, de Graaf R, Stegeman DF, & Visco YM (1992) The effect of preterm birth on brainstem, middle latency and cortical auditory evoked responses (BMC AERs). *Early human development* 31(2):113-129.
66. Inder TE, Warfield SK, Wang H, Hüppi PS, & Volpe JJ (2005) Abnormal cerebral structure is present at term in premature infants. *Pediatrics* 115(2):286-294.
67. Woodward LJ, Anderson PJ, Austin NC, Howard K, & Inder TE (2006) Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *New England Journal of Medicine* 355(7):685-694.
68. Monson BB*, et al.* (2016) Examination of the Pattern of Growth of Cerebral Tissue Volumes From Hospital Discharge to Early Childhood in Very Preterm Infants. *JAMA Pediatrics* 170(8):772-779.
69. Monson BB*, et al.* (2018) Differential Rates of Perinatal Maturation of Human Primary and Nonprimary Auditory Cortex. *eNeuro* 5(1).
70. Jobe AH (2014) A risk of sensory deprivation in the neonatal intensive care unit. *Journal of Pediatrics* 164(6):1265-1267.
71. Caskey M, Stephens B, Tucker R, & Vohr B (2014) Adult talk in the NICU with preterm infants and developmental outcomes. *Pediatrics* 133(3):e578-584.
72. Pineda RG*, et al.* (2014) Alterations in brain structure and neurodevelopmental outcome in preterm infants hospitalized in different neonatal intensive care unit environments. *The Journal of pediatrics* 164(1):52-60 e52.
73. Warren SF*, et al.* (2010) What automated vocal analysis reveals about the vocal production and language learning environment of young children with autism. *J Autism Dev Disord* 40(5):555-569.
74. VanDam M & Silbert NH (2016) Fidelity of Automatic Speech Processing for Adult and Child Talker Classifications. *PLoS One* 11(8):e0160588.
75. Zimmerman E & Lahav A (2013) Ototoxicity in preterm infants: effects of genetics, aminoglycosides, and loud environmental noise. *J Perinatol* 33(1):3-8.

76. de Vries LS, Lary S, & Dubowitz LM (1985) Relationship of serum bilirubin levels to ototoxicity and deafness in high-risk low-birth-weight infants. *Pediatrics* 76(3):351-354.
77. Johnson K, Caskey M, Rand K, Tucker R, & Vohr B (2014) Gender differences in adult-infant communication in the first months of life. *Pediatrics* 134(6):e1603-1610.
78. Mirmiran M & Ariagno RL (2000) Influence of light in the NICU on the development of circadian rhythms in preterm infants. *Seminars in perinatology* 24(4):247-257.
79. Vasquez-Ruiz S*, et al.* (2014) A light/dark cycle in the NICU accelerates body weight gain and shortens time to discharge in preterm infants. *Early Hum Dev* 90(9):535-540.
80. Mann NP, Haddow R, Stokes L, Goodley S, & Rutter N (1986) Effect of night and day on preterm infants in a newborn nursery: randomised trial. *Br Med J (Clin Res Ed)* 293(6557):1265-1267.
81. Mirmiran M, Maas YG, & Ariagno RL (2003) Development of fetal and neonatal sleep and circadian rhythms. *Sleep Med Rev* 7(4):321-334.
82. Holditch-Davis D, Scher M, Schwartz T, & Hudson-Barr D (2004) Sleeping and waking state development in preterm infants. *Early Hum Dev* 80(1):43-64.
83. Lahav A & Skoe E (2014) An acoustic gap between the NICU and womb: a potential risk for compromised neuroplasticity of the auditory system in preterm infants. *Front Neurosci* 8:381.
84. Kent WD, Tan AK, Clarke MC, & Bardell T (2002) Excessive noise levels in the neonatal ICU: potential effects on auditory system development. *The Journal of otolaryngology* 31(6):355-360.
85. Krueger C, Wall S, Parker L, & Nealis R (2005) Elevated sound levels within a busy NICU. *Neonatal network : NN* 24(6):33-37.
86. Monson BB, Lotto AJ, & Story BH (2012) Analysis of high-frequency energy in long-term average spectra of singing, speech, and voiceless fricatives. *The Journal of the Acoustical Society of America* 132(3):1754-1764.
87. Eggermont JJ & Moore JK (2012) Morphological and functional development of the auditory nervous system. *Human auditory development*, (Springer, New York), pp 61-105.
88. Al-Malky G, Suri R, Dawson SJ, Sirimanna T, & Kemp D (2011) Aminoglycoside antibiotics cochleotoxicity in paediatric cystic fibrosis (CF) patients: A study using extended high-frequency audiometry and distortion product otoacoustic emissions. *International journal of audiology* 50(2):112-122.
89. Al-Malky G, Dawson SJ, Sirimanna T, Bagkeris E, & Suri R (2015) High-frequency audiometry reveals high prevalence of aminoglycoside ototoxicity in children with cystic fibrosis. *J Cyst Fibros* 14(2):248-254.
90. Gorga MP, Kaminski JR, Beauchaine KL, & Bergman BM (1993) A comparison of auditory brain stem response thresholds and latencies elicited by air- and bone-conducted stimuli. *Ear Hear* 14(2):85-94.
91. Gorga MP, Kaminski JR, Beauchaine KL, Jesteadt W, & Neely ST (1989) Auditory brainstem responses from children three months to three years of age: normal patterns of response. II. *J Speech Hear Res* 32(2):281-288.
92. Ribeiro FM & Carvallo RM (2008) Tone-evoked ABR in full-term and preterm neonates with normal hearing. *International journal of audiology* 47(1):21-29.
93. Amin SB, Vogler-Elias D, Orlando M, & Wang H (2014) Auditory neural myelination is associated with early childhood language development in premature infants. *Early Hum Dev* 90(10):673-678.
94. Alladi PA, Wadhwa S, & Singh N (2002) Effect of prenatal auditory enrichment on developmental expression of synaptophysin and syntaxin 1 in chick brainstem auditory nuclei. *Neuroscience* 114(3):577-590.
95. Engineer ND*, et al.* (2004) Environmental enrichment improves response strength, threshold, selectivity, and latency of auditory cortex neurons. *J Neurophysiol* 92(1):73-82.
96. Moeller MP, Thomas AE, Oleson J, & Ambrose SE (2019) Validation of a Parent Report Tool for Monitoring Early Vocal Stages in Infants. *Journal of speech, language, and hearing research : JSLHR* 62(7):2245-2257.



[redacted]





**DATA SHARING PLAN**

The unique non-identifiable resources that will stem from the experiments in this proposal include ABR waveforms and other deidentified clinical data, NICU and fetal auditory exposure summary data, and survey/questionnaire data. We will seek approval from our pregnant participants to make their audio recordings publicly available contributions to day-long audio recording data bases (*e.g.*, TalkBank). Because the raw NICU recordings will include identifiable protected health information, these recordings may not be shared publicly, however summary data and acoustic measures obtained from these recordings will be made publicly available. The proposed research may result in the development of advanced acoustic analysis tools that will be made freely available. We have no proprietary interest in these tools and feel that they would be an asset to the auditory community at large. In addition, we will also provide copies of documents or samples of any materials developed under this award. In summary, any and all non-identifiable resources developed through this NIH-funded project will be made readily available for research purposes to qualified individuals within the scientific community.